Infectious Diseases: Research and Treatment

REVIEW

Update on Neglected Tropical Diseases of the Western Hemisphere

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Abstract: Neglected Tropical Diseases (NTDs) are responsible for millions of deaths and disabilities yearly, around the globe. The largest burden of these diseases falls on communities with poor access to basic sanitation, healthcare facilities, and educational programs. This review focuses on advances in vaccination, treatment and control programs over the past decade for the major NTDs of the Western Hemisphere: malaria, schistosomiasis, leishmaniasis, ankylostomiasis, lymphatic filiariasis, Chagas disease (American trypanosomiasis), and onchocerciasis.
The discussion centers on challenges for NTD eradication and prospects for the future.

Keywords: neglected tropical diseases, western hemisphere

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Introduction

Neglected Tropical Diseases (NTDs) are responsible for millions of deaths and disabilities each year, around the globe. According to the World Health Organization (WHO), the major diseases causing concern are: malaria, which affects more than one third of the world's population, including killing more than 1 million children each year; sleeping sickness (African trypanosomiasis), which affects half a million people; visceral leishmaniasis, affecting about 12 million people and Chagas disease, affecting 18 million people in Latin America alone.[1]

NTDs commonly impact the world's poorest populations, whom have inadequate access to healthcare and sanitation facilities.[2] Communities end up getting trapped in a cycle of poverty, as these diseases impair the growth of children and their intellectual development, and affect the productivity of workers. In 2002, a Global Burden of Disease study estimated that the most common NTDs, including trypanosomiasis, Chagas disease, schistosomiasis, and leishmaniasis accounted for about 1.3% of the global burden of disease and injuries.[3]

It is therefore obvious that any program that aims to eradicate NTDs must take into account the aspect of poverty.[4] Part of the United Nations Millennium Development Goals is to significantly reduce poverty by 2015. Included in this is the development of anti-poverty vaccines,[5] so called because they aim to reduce the economic burden of NTDs on worker productivity, child development, and pregnancy outcomes.[6]

In the past decade there has been a surge of interest in NTDs. The Drugs for Neglected Diseases Initiative (DNDi), funded by the Nobel Peace Prize endorsement to Medicins Sans Frontiers in 1999 was created to raise awareness of NTDs by public health advocacy and emphasis on research and drug development for malaria, visceral leishmaniasis, sleeping sickness (African trypanosomiasis) and Chagas disease.[7] Other recent global partnerships include: The Bill and Melinda Gates Foundation,[8] established in 2000, which provides funding for research and development of drugs for neglected diseases as well as public health advocacy; The Global Alliance for Vaccines and Immunization (GAVI), The Human Hookworm Vaccine initiative (HHVI), the Foundation for Innovative New Diagnostics (FIND), and the USAID funded program on integrated control of seven of the most prevalent neglected tropical diseases: trachoma, hookworm, ascariasis, trichuriasis, onchocerciasis, schistosomiasis and lymphatic filariasis.[9]

Despite this, many are disappointed with the slow progress, and argue that not enough is being done, especially on a local level, to improve the health of poor communities.[10] Often the blame is placed on pharmaceutical companies, who seem reluctant to produce economically unprofitable treatments.[11] One of the exceptions to this is the Novartis Institute for Tropical Diseases and the Novartis Vaccines Institute for Global Health, set up in 2002 and 2008, respectively, to encourage public-private partnerships for the research and development of drugs against neglected tropical diseases.[12] It further seems as if other pharmaceutical companies will need to follow suit, as recent evidence suggests a substantial geographic overlap between NTDs and the three most devastating diseases worldwide: HIV/AIDS, tuberculosis, and malaria.[13] Therefore, any attempts to eradicate these diseases must take into account NTDs as well.

This review will focus on the major neglected tropical diseases of the Western Hemisphere: malaria, schistosomiasis, leishmaniasis, ankylostomiasis, lymphatic filiariasis, Chagas disease (American trypanosomiasis), and onchocerciasis. The emphasis will be on updates over the last decade regarding vaccines, treatment and control programs. The discussion will focus on challenges as well as prospects for the future.

Vaccines

On the surface, mass vaccination appears to be the weapon of choice to control the most prevalent neglected tropical diseases. Unfortunately, several obstacles to this goal are present, including lack of funding, lack of skilled personnel to administer injections and noncompliance.[14] The most promising vaccine candidate would be one that is orally administered, cheap and insensitive to heat. Unfortunately, this is not yet an option for many of the neglected diseases.

For vaccine research purposes, the current focus is mainly on malaria, leishmaniasis, schistosomiasis and ankylostomiasis.[15]

Malaria, caused by the parasite *Plasmodium sp.*, is transmitted to humans via the *Anopheles* mosquito. After spending a brief time in the blood, it invades the

liver and damages red blood cells. It is this damage that causes the symptoms of malaria: fever, headache, joint pain, vomiting, and anemia. In severe cases, coma and even death can follow. There are five species of Plasmodium that can infect humans, and the most severe cases are caused by *P. falciparum.* Each year it is estimated that 300 to 500 million people become infected with malaria, severely impacting economic and social development of endemic areas.[15] The vaccine atovaquone/proguanil (brand name Malarone) is approved for use in travellers, although its high cost precludes its use in the general poplation.[16] Alternative vaccines, especially for children, are being developed for use in high-risk populations.[17] Currently, the most promising vaccine is one being developed by a research team headed by the University of Maryland School of Medicine's Center for Vaccine Development (CVD) and the Malaria Research and Training Center at the University of Bamako in Mali, West Africa. This vaccine is based on the *P. falciparum* membrane antigen AMA1, and is intended to boost antibodies against AMA1 mainly in children. So far, the vaccine has shown to be well tolerated and to induce sustainable, high levels of anti-AMA1 antibodies. Surprisingly, these antibody levels were sometimes higher in children who were immunized than in adults who had developed natural immunity to malaria.[18] The vaccine, which is being developed by Walter Reed Army Institute of Research (WRAIR) and GlaxoSmithKline Biologicals (GSK) holds great promise for the future.

There is currently no vaccine available for leishmania, which causes 51 000 deaths each year and 2 400 000 Disability Adjusted Life Years (DALYs) globally.[19] Leishmania is transmitted by the bite of the sand fly, and animals serve as zoonotic reservoirs. The disease comes in two forms: mucocutaneous and visceral leishmaniasis. The most common form in the Western hemisphere is mucocutaneous leishmaniasis, mainly caused by *L. braziliensis*. In the Eastern hemisphere, mucocutaneous leishmaniasis is caused by *L. major, L. tropica, and L. aethiopica.* Visceral leishmaniasis, which is the form mostly found in the tropics, is mainly caused by *L. donovani and L. infantum.* Mucocutaneous leishmaniasis results in ulcerative skin lesions which usually heal by themselves over a matter of months. In the immunocompromised, however, the disease can result in chronic disfiguration. Visceral leishmaniasis is much more severe, and damages the spleen, liver, lymph nodes and skin. It can be fatal if untreated.[15] There are several vaccine candidates for *L. braziliensis* and *L. donovani*, although clinical trials have so far been unsuccessful.[15] Main strategies involve the use of recombinant DNA-derived antigens and peptides.[20] The major challenge in developing vaccines for leishmaniasis lies in the fact that the different strains of leishmania respond differently to different vaccine preparations. Two commercial vaccines: Leish-110f, developed by BioPharm International, and Leishvacin, are potential candidates. Leish-110f has shown effectiveness in mice against *L. major* and *L. infantum* infections. Preliminary research has shown Leishvacin to prevent American cutaneous leishmaniasis caused by *L. braziliensis* in humans.[21] At this point, neither of the vaccines are in use.

Schistosomiasis, although usually not fatal, can in its chronic form cause permanent damage to internal organs, adversely affect the cognitive and intellectual development of children as well as cause bladder cancer. The disease is transmitted by larvae (cercariae), that live in water and penetrate the skin of bathers. As it develops, the parasite moves to the lungs, the liver and finally to the intestines. It completes its final stage of development in the intestines and eggs are released in the stool of the infected person. In Africa, the Caribbean, the Eastern Mediterranean and South America, the most prevalent form of schistosomiasis is caused by *Schistosoma mansoni*. This form of schistosomiasis is characterized by severe intestinal obstruction, liver failure, and potentially fatal gastrointestinal or esophageal bleeds.[15] The Sabin Vaccine Institute launched a schistosomiasis vaccine initiative in 2008. The antigen used for development of the vaccine, Sm-TSP-2, is intended for use in conjunction with praziquantel drug therapy, which kills the worm, in order to provide optimum immunity. So far, the results have been promising and pre-clinical studies on the vaccine candidate are taking place in 2010.[22,23]

The Human Hookworm Vaccine Initiative (HHVI), established in 2000 by the Sabin Vaccine Institute, aims to develop a recombinant vaccine that confers immunity to hookworm. Human hookworm infection (ankylostomiasis), caused by nematode parasites *Ancylostoma duodenale* and *Necator americanus*, is

one of the leading causes of anemia and malnutrition in impoverished areas. In school aged children, this may cause growth retardation and learning disabilities.[24,25] The hookworm is an intestinal parasite, which belongs to a family known as the soil-transmitted helminths (STH). The method of infection is an unusual one: larvae penetrate the skin of the foot, migrate through the blood vessels to the lungs, and up to the trachea. Once in the trachea, they are swallowed, pass down the digestive tract and live in the intestine of the host, feeding on blood and depleting the host of vital nutrients. Immunization with the most promising vaccine antigen candidate, *Na*-ASP-2, intends to reduce the rate of larval hookworm migration to human body tissues. It has undergone Phase 1 safety trials in the USA in 2006 and Brazil in 2007–2008.[26] Another vaccine being developed by the Sabin Vaccine Institute aims at interfering with hookworm blood feeding at the site of attachment in the intestine. In order to do this, the human immune system must be stimulated to produce antibodies that inhibit parasite blood feeding. Two antigen candidates are under way for this strategy: *Na*-GST-1, which is scheduled for clinical testing in 2010, and *Na*-APR-1, which will be tested in 2011.[26]

Treatment

The majority of treatment options available today for neglected tropical diseases are unfortunately old and poorly tolerated. For instance, African trypanosomiasis is still treated with the poison arsenic, and leishmaniasis is treated with toxic antimonials. In an article, Dr. White argues that this would not be the case if these diseases had been endemic in more developed countries, where funding would not be the limiting factor for drug development.[27]

Of the diseases focused on in this paper, most of the advances in treatment center on malaria, schistosomiasis, lymphatic filariasis, and Chagas disease. As with any treatment program, the main issues continue to be cost, compliance, and possibilities of drug resistance. The challenge therefore lies in developing a drug that will be well tolerated, cheap, and simple to use.

Several malaria-endemic areas of the Western Hemisphere, including Venezuela, Colombia, Brazil and Ecuador, still struggle with chloroquine resistance.[28] No strain of *Plasmodium* has yet developed resistance to artemesinins, which remain the gold standard for treatment of complicated malaria.[29] However, since pure artemesinins should only be used in extreme cases, to avoid risks of future resistance, the WHO recommends the use of so-called artemesinin combination therapies (ACTs) instead.[30,31] A new ACT that is currently being tested involves the use of dihydroartemesinin (DHA), which is an active metabolite of artemesinin derivatives, combined with piperaquine (PQP), a compound similar to chloroquine. The dosing is fairly simple: one single daily dose over three days.[32] This represents a significant improvement to the dosing required for the more commonly used artemether-lumefantrin combination treatment, which requires twice daily administration together with fatty food. Adverse events of the DHA-PQP were reported to be rare and mild, including abdominal pain and diarrhoea. The cost of manufacturing the new drug would be relatively low, and it is considered a potential future treatment option for endemic areas.

Praziquantel is currently the treatment of choice for schistosomiasis caused by *Schistosoma mansoni*. Although it is relatively cheap and effective, concerns about resistance mean that new drugs are being considered. A major target for new drugs is cysteine proteases, which play important roles in schistosome metabolism, including digestion, reproduction, and protein turnover. In mice experiments, the compound K11777 was shown to inhibit the activity of schistosome-specific cysteine proteases, and may be a candidate for a new line of drug.[33]

Lymphatic filiariasis (LF) is caused mainly by the worm *Wuchereria bancrofti*. It is transmitted by mosquitoes and the adult worm lives in the host's lymphatic system, effectively blocking the flow of lymph. In extreme cases, this can cause elephantiasis, a disease in which the lower limbs swell to an extent where normal activities are severely impeded. In addition, this often causes social stigmatization as well as sexual and work-related disabilities.[34] The disease course of elephantiasis is due in part to a symbiotic bacterium, *Wolbachia*, and in part to the host immune system's response to the infection, both of *Wuchereria bancrofti* and of *Wolbachia*. One third of the people infected with LF live in South Asia, the Pacific and the Americas.[35] In the Western Hemisphere, the treatment for LF is a combination of diethylcarbamazine

and albendazole.[36] Unfortunately, these drugs are ineffective against adult worms, which are the ones that cause disease.[37] Recently, it has been shown that a 4 week course of the antibiotic doxycycline, which is used to treat infection with *Wolbachia*, is also effective at killing adult *Wuchereria* worms.[37] In one study, doxycycline even halted the progression of lymphedema and reversed it in the early stages.[38]

Chagas disease, caused by the protozoan *Trypanosoma cruzi*, is transmitted by the triatomine bug. Infection with *T. cruzi* causes a local swelling at the site of infection. After a chronic, asymptomatic phase, 40% to 50% of patients develop progressive cardiomyopathy and/or motility disturbances of the esophagus and colon.[39] The currently available chemotherapeutic agents for Chagas disease are benznidazole and nifurtimox. Although beneficial in the acute stage of the disease, the drugs are generally considered ineffective in its chronic stage. In addition, both drugs are associated with significant adverse effects including hepatitis and neurotoxicity.[40] A challenge to the treatment of chronic symptoms of Chagas disease is that manifestations often differ according to geographic location. For instance, in Brazil, esophageal complications are more common than large bowel pathologies, whereas in Chile, it is the opposite. Cardiomyopathy, however, is prevalent in both regions.[41] At present, the drugs posaconazole, an antifungal agent, and amiodarone, an antiarrhythmic drug, have both been used successfully in the treatment of Chagas disease related cardiomyopathy.[40] Two drugs that specifically target the chronic manifestations of Chagas disease are currently under development: one is K777, which has been shown to lower levels of parasitemia and to improve cardiac function in dogs, and the other is DB766, which is active at low temperatures and is therefore an option in the treatment of donated blood suspected of being infected with *T. cruzi*.[40] Apart from surgery, there is as yet no definitive treatment for the gastrointestinal manifestations of the chronic condition.

Control Programs

Any successful control program must be willing to address the issue of social stigma that often prevents communities from discussing diseases deemed as "embarrassing". Often, such stigma comes from the misreading of Biblical accounts, for instance of leprosy, a disease thought to afflict those with immoral behaviour. Important NTDs for which stigma exist include onchocerciasis, lymphatic filiariasis, plague, Buruli ulcer, leishmaniasis, and Chagas disease.[42] Weiss recounts the story of a 25 year old woman in Uganda who describes the shame felt by a member of their community afflicted with dermatitis. The patient was considered dangerous, shunned by the community and hidden in order not to be seen. Such attitudes need to be addressed and public awareness, adequate knowledge and understanding is the only way in which myths like these can be dispelled.

Another substantial challenge that exists when considering control programs is polyparasitism, which often appears to be the norm rather than the exception in developing countries. To overcome this, Utzinger et al,[43] propose an integrated intervention approach, wherein parasites that can be eliminated with a similar technical approach, can be co-targeted. Hotez et al[44] suggest deploying four oral drugs: albendazole, azithromycin, ivermectin and praziquantel, which will target over 90% of the neglected diseases.

Polyparasitism is most effectively combated with a so-called rapid-impact package of drugs. These drugs can quickly be deployed by community-based distributors to areas in need. The proposed package includes a combination of four out of six drugs: albendazole or mebendazole, praziquantel, ivermection or diethylcarbamazine, and azithromycin.[45]

The most common methods for control of the NTDs are: targeting the vectors of the infectious organism or mass drug administration. The main NTDs for which vector control has been employed are Chagas disease and malaria. Mass drug administration, on the other hand, has been used to combat lymphatic filiariasis and onchocerciasis.

In Brazil, the Chagas Disease Program has demonstrated great success in reducing the prevalence of the disease. In the 1940s, the main strategies for controlling Chagas disease centered on housing improvement and insecticide spraying. National control programs were implemented after the 1970s. In 1991, the Southern Cone Initiative was launched. This program has successfully eliminated Chagas disease transmission in Uruguay, Chile, and large parts of Brazil and Argentina.[46] By covering endemic areas with regular insecticide spraying, the number of deaths due to Chagas disease have dropped during the past two

decades in Brazil from 5 per 100 000 inhabitants to 3.5 per 100 000 inhabitants.[47]

In the 1940s to the 1960s, the main method for malaria control in endemic areas was regular spraying of houses with the insecticide DDT. This strategy was very helpful in reducing the rates of malaria, especially in many South American countries. Since then, DDT has been associated with adverse health effects and many governments and donors have showed declining interest in this method. The net effect has been the rise of malaria in several areas, including Brazil, Peru and Guyana.[48,49] Today, about 36% of the population of the Americas live in malaria-endemic areas, including around 293 million people in 21 endemic countries. During 2000, 87% of the total cases of malaria (1.14 million), were recorded in the Amazonian sub region of South America.[50] The most common alternative to DDT is the use of bed nets impregnated with insecticide. This is an effective strategy for mosquitoes that feed at night, including most species of *Anopheles* mosquito, that transmit malaria in sub-Saharan Africa. However, in the Amazon, the primary malaria vector, *A. darlingi*, has a peak biting activity between 8 pm and 10 pm. This means that more than 80% of feeding occurs before most local people go to bed, where they can be protected by a treated bed net.[51] To combat malaria in these areas, it is recommended that the local population employ regular use of insecticide spray and lotions containing eucalyptus-based repellent or DEET.[52] However, the sprays are costly and non-compliance is a major issue, leading many to call for the reinstatement of DDT use, despite its adverse effects.[53] An exciting new approach to the control of malaria comes from the use of genetically modified mosquitoes. The principle behind the use of such mosquitoes is the alteration of critical genes which will prevent *Plasmodium* from developing in the mosquito.[54] There are two main potential targets for genetic modification: paratransgenesis, which is the genetic manipulation of commensal bacteria in the gut of the mosquito, blocking parasite invasion or directly killing the parasite; and genetic modification of mosquitos themselves to express proteins that interfere with *Plasmodium* development.[55] To date, the most promising approach centers on the latter principle. A team of researchers at the University of Arizona recently demonstrated that an increase in the expression of a specific protein kinase called Akt, involved in insulin signaling, could dramatically reduce *Plasmodium* development in the mosquito. In addition, overexpression of this protein kinase also reduced the average lifespan of the infected mosquito, limiting the possible time frame for transmission.[56] The next step in development of an effective vector control system such as this is to generate a way to introduce the modified mosquitoes into the natural population. As yet, there is no conclusive evidence to suggest that the genetically modified mosquitoes have enhanced fitness compared to the native mosquito population, and further modifications need to be made to ensure this.[57] Finally, genetically modified technology is in general the subject of intense controversy on social, ethical and legal platforms. All of these challenges need to be addressed and resolved before the use of genetically modified mosquitoes can become routine.

Through mass drug administration, the Global Programme to Eliminate Lymphatic Filiariasis aims to eliminate LF as a public health problem by 2020. The drugs used in the Western Hemisphere are albendazole and diethyl-carbamazine, which are to be distributed to about 80% of the entire at risk population annually for four to six years.[58] To date, 442 million doses of albendazole tablets, 399 million ivermectin tablets and 499 million DEC tablets have been donated to WHO. By 2005, approximately 610 million people in 42 countries were reached by the program, representing about 50% of the at-risk population. Efforts are also under way to provide increased access to hydrocele surgery at the district level and lymphedema management training for community home based self care.[59] Since its institution in 2000, studies have been made on the effectiveness of the program, but insufficient data about LF incidence before its implication make it difficult to infer any effects. The only country in which adequate data existed both before and after the institution of the program, is Niue in the Pacific, where there was a remarkable decrease in the incidence of lymphatic filiariasis after the initiation of a mass drug administration program.[60]

Onchocerciasis, also known as "River Blindness", is caused by the roundworm *Onchocerca volvolus.* Its reservoir is the blackfly of the genus *Simulium*. Onchocerciasis is the world's second leading infectious cause of blindness.[58] Like LF, the cause of morbidity is not the parasite itself, but its endosymbiotic

Wolbachia bacterium. As the worm dies, *Wolbachia* is released, causing an immune response that damages nearby tissues, especially the eye. Treatment for onchocerciasis involves the drug ivermectin, which kills the larval form of the roundworm. The Mectizan Program for the Control of onchocerciasis, started in 1987, is an effort by the pharmaceutical company Merck, to donate as much ivermectin as needed for as long as necessary to eradicate onchocerciasis in endemic regions. This program has been effective, and from 1988 to 2007, Mectizan has been approved for use in over 570 million treatments.[61]

Discussion

Most of the countries in the Western Hemisphere struggling with neglected tropical diseases are in Latin America and the Caribbean. Poverty is by far one of the main reasons why neglected tropical diseases continue to persist in these areas. Poor resources mean that sanitation facilities are often scarce and poorly maintained. In addition, there is inadequate use of footwear as well as insufficient hygiene practices.[62] In 2008, the WHO/UNICEF Joint Monitoring Program for water supply and sanitation declared sanitation as its central focus. The sanitation coverage of Latin America and the Caribbean has increased from a 68% coverage in 1996 to a 79% coverage in 2006. Unfortunately, Bolivia, the poorest nation in the region, is not on track with these goals.[62] Improving sanitation in areas that are endemic in NTDs would significantly reduce disease burden.

Lack of funding continues to be the main obstacle in the path to eradicating neglected tropical diseases. Global partnerships have made significant contributions to the research on neglected diseases, but without support from local government, the results have only been moderately successful.[63]

Further, it is important to realize that we cannot eradicate the "big three": tuberculosis, malaria and HIV/AIDS without focusing on the neglected diseases as well. Often these diseases will occur together with neglected diseases and increase the morbidity and mortality associated with parasitic infections.[64] Other important issues to address include the social stigma attached to several of the neglected diseases, and the ignorance of their transmission and origin. These issues need to be dealt with on a public advocacy level before we can begin to see any change. However, there is hope for the future. In the fields of drug development, vector control and disease prevention, promising results are starting to emerge and the hope is that research will continue to yield sustainable practices to eradicate neglected tropical diseases, once and for all.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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