**Neglected Tropical Diseases**

**Introduction**

The Neglected Tropical Diseases (NTDs) were introduced as a new entity in tropical medicine in 2005 in a response to all the attention the “big three”: malaria, tuberculosis and HIV/AIDS received in particular after the creation of the Global Fund to Fight AIDS, tuberculosis and malaria, in 2002. This has caused these important diseases to receive and attract funds, and resulted in an enormous drive to develop new tools for their control in particular drugs; numerous private-public partner ships and multiple large scale interventions has saved millions of lives.

However, a long list of other diseases were receiving even less attention than before as a result of this diversion and concentration of efforts and funds. The NTDs that affect 1 billion people, include classical tropical diseases such as Human African Trypanosomiasis (HAT) and leishmaniasis that were still treated with old and toxic drugs containing heavy metals including arsenic (melarsoprol in HAT) and antimony (stibogluconate in leishmaniasis) and that were developed decades ago. A systemic review covering a 25-year period showed virtually no new chemical entities for tropical diseases in contrast to drugs for cancer and neurological diseases. [1] Similarly diagnostic tools remained inadequate. The list is of course much longer and the current list includes 40 diseases including helminthic, parasitic, bacterial, ectoparasitic and fungal diseases (Table 1). Common characteristics are that they are chronic, debilitating and stigmatizing diseases that affect the poorest segment of populations that live in remote areas. They have a profound effect on poverty and social and intellectual development thus causing a vicious circle. Lack of access to safe water, poor sanitation and poor housing are important contributing factors. There are major difficulties in estimating the global burden of the NTDs in DALYs; recent estimates are 56.6 million DALYs for NTDs compared with 46.5 million for malaria and 34.7 million for tuberculosis. Actual estimates for NTDS may be much higher and currently new estimates are being collected.

**Important players and developments**

Médecins sans Frontières (MSF) was among the pioneers to draw attention to the lack of drugs for the neglected diseases and brought together 7 partners [among these: the Pasteur Institute, the Kenya Medical Research Institute (KEMRI) and WHO/TDR (special programme for Research and Training in Tropical Diseases)] to establish the Drugs for Neglected *initiative* (DND*i*), based in Geneva, in 2003. On a similar note, the Bill and Melinda Gates Foundation (BMGF) provided a grant to establish the Foundation for Innovative and New Diagnostics (FIND), also in Geneva, in 2003. While initially focusing on new diagnostics for tuberculosis, FIND now addresses neglected conditions such as HAT, Chagas’ disease and leishmaniasis.

The World Health Organization (WHO) has also adapted to these developments and a Neglected Tropical Diseases department was established; on their website now feature 17 diseases and another 4 that are recognized as NTDs but that receive limited though important support such as collection of epidemiological data and production of guidelines. [3] Mycetoma was the last addition to this list in July 2013. To qualify as an NTD the WHO has published a number of criteria that should be met:

* A proxy for poverty and disadvantage
* Affect populations with low visibility and little political voice
* Do not travel widely
* Cause stigma and discrimination, especially of girls and women
* Have an important impact on morbidity and mortality
* Are relatively neglected by research
* Can be controlled, prevented and possibly eliminated using effective and feasible solutions

The WHO-TDR (special programme for Research and Training in Tropical Diseases) has a new 10- year strategic plan. Funding is increasingly available from BMGF, Wellcome Trust, the NIH and US and UK governments. Neglected diseases are in their portfolio.

A number of public – private partnerships provide free drugs such as for onchocerciasis (ivermectin), filariasis (albendazole) and azithromicin (trachoma).

International journals have also increasingly embraced NTDs and more than 1600 papers have been published by September 2012. [2] The Public Library of Science launched the PLoS Neglected Tropical Diseases journal as one of its open-access journals.

**Research in Neglected Tropical diseases**

Who is working in neglected diseases research? A complete overview of research activities in NTDs in the Netherlands is beyond the scope of this article. Traditionally, schistosomiasis research has been strong in Leiden University Medical Centre (LUMC), while the Erasmus MC continues to play a leading role in basic science research in mycetoma. More recently a much needed research line has been introduced in the field of pharmacokinetics and pharmacodynamics of drugs used in leishmaniasis, supported by DNDi, first in the AMC in Amsterdam and now in the University Medical Centre in Utrecht.

In the past decade the face of tropical medicine has changed. While classically this was the business of some universities and tropical medicine schools, non-governmental organizations such as MSF have taken an important role. By nature of their mandate they are working in the field and in remote areas and as such they have exposure to a whole range of tropical, infectious and non-infectious conditions. While 20 years ago research was felt by many MSF workers as not part of their mandate this fortunately changed as there was a need for improved diagnosis, treatment etc. for better management of the conditions they encountered. In addition it was felt that the organization had a moral duty to make optimal use of their strong presence in the field and carry out research with or without other partners. Now we have numerous examples of excellent contributions to the management of a variety of conditions. Indeed MSF is now a leading player in the whole field of tropical medicine research.

Another good example is DNDi that was founded by MSF (and other partners) to address the issue of lack of drugs for the neglected diseases. DNDi has developed new treatments for leishmaniasis that are easier to administer, with shorter duration and less side-effects. In East Africa a combination therapy of SSG and paromomycin for 17 days has now replaced monotherapy with stibogluconate for 30 days. New compounds are in the pipeline such as fexinidazole. Another example is the introduction of nifurtimox - eflornithine combination therapy (NECT) for HAT reducing the duration of monotherapy with eflornithine infusions from 14 days (4 times for day) to 10 days (twice per day only), in combination with nifurtimox as an oral treatment, with similar efficacy. Other conditions in the research agenda are paediatric HIV treatment, filiarial diseases and Chagas’ disease. [4]

In January 2013, a collaborative disease eradication programme was launched that is committed to eradicate, eliminate or control 10 NTDs. This so-called London Declaration on Tropical diseases was endorsed by, among others, the WHO, the World Bank, DNDi, USAID, leading pharmaceutical companies and the BMGF. [5]

**The future**

While the advocacy for NTDs has been successful and already a lot has been achieved, a new set of conditions are now more and more coming into the picture: the non-communicable diseases that are more seriously neglected and for much longer than any other group of conditions. Hypertension, diabetes mellitus, and heart failure (from whatever cause) are common throughout the tropics and may become even more important as urbanization increases with changes in dietary habits etc. A different approach is needed here; for example for diabetes the drugs needed are largely there; the problem is in patient education, improved nursing care and ensuring uninterrupted drug delivery. This also applies to hypertension and heart failure, but here there is a pressing need to carry out research studies as the tremendous amount of knowledge on hypertension and heart failure comes from studies in western populations. These do not necessarily apply to non-causacian populations as was shown in studies in the USA when comparing results in white and black Americans.

The advance of neglected diseases will be unstoppable; they are fashionable and attract attention in the media and therefore donors are more and more interested. This may be at the expense of other conditions; some already fear that the big three (malaria, HIV/AIDS and TB) are now at risk of becoming neglected. And now the non-communicable conditions are starting to compete for the limited funds available, the principal reason for this unnecessary dividing up of tropical medicine in categories.

Literature

1. [Trouiller P](http://www.ncbi.nlm.nih.gov/pubmed?term=Trouiller%20P%5BAuthor%5D&cauthor=true&cauthor_uid=12090998), [Olliaro P](http://www.ncbi.nlm.nih.gov/pubmed?term=Olliaro%20P%5BAuthor%5D&cauthor=true&cauthor_uid=12090998), [Torreele E](http://www.ncbi.nlm.nih.gov/pubmed?term=Torreele%20E%5BAuthor%5D&cauthor=true&cauthor_uid=12090998), [Orbinski J](http://www.ncbi.nlm.nih.gov/pubmed?term=Orbinski%20J%5BAuthor%5D&cauthor=true&cauthor_uid=12090998), [Laing R](http://www.ncbi.nlm.nih.gov/pubmed?term=Laing%20R%5BAuthor%5D&cauthor=true&cauthor_uid=12090998), [Ford N](http://www.ncbi.nlm.nih.gov/pubmed?term=Ford%20N%5BAuthor%5D&cauthor=true&cauthor_uid=12090998). Drug development for neglected diseases: a deficient market and a public-health policy failure. Lancet 2002; 359:2188-94.

2. Utzinger J, Becker SL, Knoppa S,Blum J, Neumayr AL, Keiser J, Hatz CF. Neglected tropical diseases: diagnosis, clinical management, treatment and control. Swiss Med Wkly. 2012;142:w13727

3. [www.who.int/neglected\_diseases/en](http://www.who.int/neglected_diseases/en)

4. [www.dndi.org](http://www.dndi.org)

5. www.UnitingTo CombatNTDs.org

Table. Neglected Tropical Diseases

Fungal diseases

 Mycetoma

 Paracoccidioidomycosis

Viral diseases

 Dengue

Japanese encephalitis

Yellow fever

Rabies

Rift Valley fever

Viral haemorrhagic fevers

Bacterial infections

 Bartonellosis

Bovine tuberculosis in humans

Buruli ulcer

Enteric bacterial infections: cholera, ETEC, shigellosis, salmonellosis

Leprosy

Leptospirosis

Relapsing fever

Trachoma

Treponematosis

Ectoparasitic infections

 Myiasis

Scabies

Helminthic infections

Cysticercosis

Dracunculiasis

Echinococcosis

Enterobiasis

Food-borne trematodiasis: Clonorchiasis, Fascioliasis, intestinal flukes infections, Opisthorchiasis, Paragonimiasis

Loiasis

Lymphatic filariasis

Mansonellosis

Onchocerciasis

Schistosomiasis

Soil-transmitted helminthiaisis

Ascariasis, hookworm infection, Strongyloides,Trichuriasis

Toxocariasis

Protozoal infections

Chagas’ disease

Human African Trypanosomiasis (HAT)

Intestinal protozoan infections: Amoebiasis, Balantidiasis, Giardiasis

Leishmaniasis