FILARIAL DISEASES

Foot measurement of a lymphatic filariasis patient in Sukala, Satyavadi, Puri district, Odisha, India.

› **The helminth** worms responsible for causing parasitic disease in animals and humans are classified into three species – roundworms or nematodes (including filarial worms and soil-transmitted helminths), flatworms, and flukes. Filarial worms are spread by blood-feeding insect vectors, and invade different parts of the human body causing chronic disease. *Wucheria bancrofti*, *Brugia malayi*, and *B. timori* adult worms invade the lymphatic system, and *Onchocerca volvulus* and *Loa loa* form deep tissue and subcutaneous nodules.

Onchocerciasis is predominantly found in West and Central Africa where it causes river blindness, so-called because the black flies which spread disease breed in fast-flowing rivers and streams, and can produce blindness after many years of chronic infection. Before large control programmes started, blindness was highly prevalent in villages along rivers infested with blackflies, leading to the abandonment of fertile land, and increased poverty. An estimated 37 million people are infected with *O. volvulus* worms, which cause severe itching and may result in blindness or impaired vision.

Lymphatic filariasis (LF) is more widespread, found in tropical areas principally in Africa and Asia. Worms migrate to the lymph glands, resulting in swollen limbs and genitals, a disabling, painful, and highly stigmatizing affliction. Over 67 million people are infected and over 36 million are estimated to be clinically affected by the symptoms.

Loiasis, also known as African eyeworm because of the migration of the adult worm through the conjunctiva, has less direct impact, with symptoms not considered to be as severe. But loiasis infection has important implications for LF and onchocerciasis control programmes using preventive mass drug administration (MDA) chemotherapy, as serious adverse events can occur in co-infected patients.

MDA programmes depend on donations from pharmaceutical companies, and although the drugs are effective in killing the different juvenile worms (microfilariae) of the *O.volvulus*, *W. bancrofti*, and *Brugia* worms, they do not kill adult worms (macrofilariae) which continue to reproduce during most of their long lifespan. MDA chemotherapy therefore needs repeating once or twice annually for over a decade. A short-course treatment that kills adult worms is needed to cure patients, and may also be useful in reducing the number of cycles of MDA to achieve disease control or elimination.

Treatments are needed for juvenile as well as adult worms

DND*i* is aiming to develop a safe and effective field-adapted macrofilaricidal drug with its partners, based on drugs used to treat animal helminth infections. A parallel approach is to target *Wolbachia*, a symbiotic intracellular bacterium present in *Onchocerca*, *Wucheria*, and *Brugia* worms, aiming to identify drugs which kill the *Wolbachia* and impact worm survival and reproduction.

The year 2015 was a defining one for filarial diseases. In October, one half of the Nobel Prize for Medicine was awarded jointly to William Campbell and Satoshi Omura for their discovery of the antifilarial drug ivermectin, used in MDA programmes. Meanwhile, the 20-year old African Programme for Onchocerciasis Control, considered to be one the most successful public health initiatives ever, closed at the end of the year. While both milestones bear testament to the progress made in treating these diseases, millions of people remain affected and in need of a curative treatment.

What are the current treatments and their limitations?

Current treatments for onchocerciasis and lymphatic filariasis are based on repeated mass drug administration (MDA) of antiparasitic drugs through programmes directed by the WHO. WHO recommends MDA for onchocerciasis at least once yearly for 10-15 years, and for lymphatic filariasis once yearly for at least five years. The drugs used in MDA programmes are ivermectin for onchocerciasis;albendazole for lymphatic filariasis; and albendazole plus either ivermectinin areas where onchocerciasis is also endemic (i.e. African countries), or diethylcarbamazine(DEC) in areas where onchocerciasis is not co-endemic (i.e. non-African countries).

A bite from an infected insect allows filarial larvae to pass into the blood and migrate through the human body. These mature into adults that produce microfilariae, which the insect ingests during a blood meal, and the cycle goes on. MDA drugs can prevent this vector-borne transmission for several months by killing mainly the microfilariae, and inducing a temporary sterilization of adult worms. However, because adult worms (macrofilariae) continue to live in the body, they eventually produce new microfilariae, often before the next MDA, thus requiring repeated MDAs for several years to decades.

Ivermectin treatment is safe and has been used widely in MDA programmes. However, the use of ivermectin in patients co-infected with high levels of *Loa loa* microfilaria in the blood can result in safety issues such as the occurrence of encephalopathy that can be fatal if not properly managed. Additionally, a suboptimal response to ivermectin in patients with onchocerciasis has been reported which may be a sign of resistance development. Furthermore, the morbidity associated with onchocerciasis and LF infection (itching, dermatitis, lymphedema, and blindness) are only partially improved or prevented and require repeated treatment with the current drugs.

ONCHOCERCIASIS

37 million infected worldwide, with 99% cases in **31 African countries**

746,000 visually impaired

265,000 blinded and more than 4 million suffering from severe itching

169 million were estimated at risk in 2014

LYMPHATIC FILARIASIS

Over **1.1 billion** people at risk worldwide, 57% in South East Asia region

Over **36 million** suffering from clinical illness (19.4 million with hydrocele, and 16.6 million with lymphedema)

WHAT IS DND *i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

DND*i*'s strategy is to develop a new compound with macrofilaricide activity (to kill adult worms) for use as a safe and field-adapted macrofilaricidal drug for patient case management and possibly later MDA if needed.

As a medium-term strategy, DND*i* is assessing emodepside which is commercialized by Bayer under license from Astellas as an anthelmintic veterinary drug for cats and dogs in combination with praziquantel (Profender®) and in combination with toltrazuril (Procox®). DND*i* has an agreement with Bayer to develop emodepside for the treatment of onchocerciasis.

Other compounds targeting Wolbachia a worm symbiotic bacteria present in the parasites causing onchocerciasis and LF, will also be explored.

As a long-term strategy, DND*i* is assessing additional opportunities through an active screening programme of drug compounds emanating from animal health/pharmaceutical companies and academic institutions, with the goal of selecting one or two candidates to move into clinical development.

DND*i* aims to deliver a safe, efficacious, affordable, and field-adapted macrofilaricidal drug for onchocerciasis and/or lymphatic filariasis for the treatment of patients, and as a possible alternative in mass drug administration programmes.

DNDi
Drugs for Neglected Diseases *initiative*