

Neglected tropical diseases: A new handle on old problems

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‘Neglected tropical diseases’ is a new name for old diseases that cause long-term suffering among the world’s poorest people. The Wellcome Trust and others have funded research into these diseases for decades, but the fruits of this research have not always reached the people most in need. Michael Regnier spoke to some of the scientists who coined the new phrase to raise awareness of the continuing burden of these diseases, and to Trust-funded researchers whose work is helping to develop better solutions for tackling them.

The 'big three' infectious diseases in global health are the all too familiar HIV/AIDS, malaria and tuberculosis. Less well known are a host of other infections endemic across the world.

Caused by a motley variety of parasites, viruses and bacteria, these diseases are a serious problem in low- and middle-income countries, causing deaths, long-term disability and disadvantage. They are diseases

of poverty, mostly affecting the world's poorest nations and trapping their people in a cycle of economic stagnation, but they do not receive anything like the attention or funding given to work on the big three.

In the past five years or so, wider attention has begun to fall on these other diseases, thanks largely to a campaign led predominantly by scientists and centred on a new name: 'neglected tropical diseases', or NTDs.

"The phrase was part of a drive to think about these diseases in a fresh light," says Professor Peter Hotez, President of the Sabin Vaccine Institute in Washington, DC, and Editor-in-Chief of the journal '*PLoS NTDs*'. "After the launch of the Millennium Development Goals in 2000, a lot of attention fell on HIV, tuberculosis and malaria. Goal 6 called for action on those three 'and other diseases'.

"It led to a lot going on in HIV, tuberculosis and malaria, but those of us working on the 'other diseases' felt we were on the outside looking in. We were driven to think afresh, to 'rebrand' these conditions."

Hotez's research is on vaccines for human hookworm infection and other parasitic worms. As with many NTDs, they are not lethal in themselves but infections can last for decades, impairing children's growth, development and physical fitness and causing severe anaemia during pregnancy, which leads to low birth weight and increased infant and maternal mortality.

"The most common [neglected tropical diseases](#) have high morbidity and low mortality," explains Hotez. "They are causes of poverty through their effects on children, pregnant women and workers. From descriptions in ancient texts, we know these diseases have been around for ever. They are the opposite of emerging diseases."

We are more scared of emerging diseases, Hotez suggests, but NTDs do more harm overall.

Definitions of neglect

'Neglected tropical diseases' is not a precisely defined term. Not all NTDs are exclusively tropical, and the nature of 'neglect' varies. Sometimes neglect comes from the communities in which these diseases are found: lymphatic filariasis, for example, causes severe disfigurement and massively swollen limbs, which can lead to prejudice and stigma.

In other cases, neglect is from richer nations, where diseases such as schistosomiasis and dracunculiasis are unfamiliar and infections such as cholera and leprosy are chapters from history rather than pressing medical problems.

It doesn't help that the available information about how many people are infected or dying from these diseases is not always reliable. NTDs are more common in regions of extreme poverty or conflict - not situations that lend themselves to effective epidemiological monitoring.

Research into NTDs may have been neglected too. The Wellcome Trust has consistently funded research on tropical diseases and currently spends a significant proportion of its funding on global health research, and the World Health Organization (WHO) established its Special Program for Research and Training in Tropical Diseases (TDR) in 1975.

Other major health challenges were competing for attention in the latter half of the 20th century, however - including emerging infections and the rising incidence of cancer and cardiovascular disease. Meanwhile, the pharmaceutical industry cut programmes on parasitic infections, for example, because there wasn't a profitable market to invest in.

Frustratingly for those scientists who were researching NTDs, effective drugs were already available for a small number of them but were not being widely used. Even when drug companies began donating these drugs or supplying them at very low cost for use in lower-income countries, simple cost-effective programs to implement mass drug administration often struggled to find sustained funding.

Proof of principle

Professor Alan Fenwick, Director of the Schistosomiasis Control Initiative (SCI) at Imperial College London, worked in Egypt for 15 years. In that time, the prevalence of schistosomiasis there fell from 20 per cent to less than 5 per cent. He knew it was possible to reduce the burden of the disease until it was no longer a public health issue; his problem was in finding the support to apply this knowledge in other countries.

"Many organizations are interested in supporting research; some, like the Wellcome Trust, are mandated to only fund research," says Fenwick. "But this left schistosomiasis and others in limbo: most of the research had been done. We had the tools which, if implemented properly, could help some 200 million people in sub-Saharan Africa."

In 2002, he approached the Bill & Melinda Gates Foundation and suggested they buy and distribute praziquantel, an effective schistosomiasis drug treatment, in countries where the disease was endemic.

"They agreed to allow me to test the proof of principle: 'Will these countries implement control if given access to drugs and funding?'"

Fenwick was awarded \$30m to work with African countries to introduce national programmes to control schistosomiasis. The first treatment

began in Uganda in 2003 and after one year, the intensity of schistosome infection had fallen by 70 per cent. Disease control is an ongoing challenge, however: "If we stop treating," he says, "I fear that within five years it will come back again."

The SCI has supported or is currently working in 12 African countries and is still expanding coverage. More than 100 million people have been treated at least once. Moreover, it treated people for three parasitic worm infections at the same time, effectively tackling four NTDs with one integrated programme.

Drug development for NTDs

Programmes such as the SCI are successful not only because the drugs are donated or provided at low cost but also because the drugs are safe and effective and can be given orally in a single dose every six or 12 months.

The drugs available for many other NTDs are not so practical, and there is a desperate need to discover new treatments. Wellcome Trust funding continues to contribute to every step of this process.

Professor Alan Fairlamb, Co-Director of the Wellcome Trust-funded Drug Discovery Unit at the University of Dundee, agrees that only a handful of current NTD drugs are truly fit for purpose: "Many compounds were developed with a different indication in mind, maybe from cancer research or antifungal drug discovery programs. The target product profile for these original indications does not take into account the association with poverty and the rural setting where most NTD drugs are needed.

"One thing frequently missing in the equation from the pharma perspective is low cost of goods," he adds. "Expensive drugs are good for

the odd safari but too costly for the local population. People often can't afford the treatment, so they don't complete the course and this drives resistance. The challenge is to develop cheaper and safer drugs."

The Dundee Unit works on the best potential targets wherever they come from, making concepts viable for further development in animal models. Fairlamb says they are always looking for scientists with a promising target but who don't have either the know-how or the infrastructure to do drug discovery. "Our vision is to take excellent basic science and turn it into useful medical products," he says.

Their most successful project to date is based on an enzyme called N-myristoyltransferase (NMT), which was developed as a target at Imperial College London by Professor Deborah Smith, now at the University of York. The enzyme has been found in several parasites: the Dundee Unit is working on developing a drug for human African trypanosomiasis (sleeping sickness) while Smith, also with funding from the Wellcome Trust, is leading on developing drugs and vaccines for leishmaniasis. NMT may even be a target for new malaria drugs.

"There's still a long way to go," Smith says, but even if the work on NMT does not lead to a viable drug for all these diseases, it will be valuable research. "We're doing the groundwork for future potential opportunities," she concludes.

Approaching the problem from all angles

Some NTDs have no effective drugs or vaccines. Dengue virus, for example, causes fluid to leak from blood vessels into surrounding tissues, leading to severe shock in some cases. The only available treatment is to replace the fluid in hospital, which puts a huge burden on health systems during outbreaks.

"Dengue is neglected in the sense that the true scale of the disease burden is poorly understood and certainly underestimated," says Professor Cameron Simmons, a Wellcome Trust Senior Research Fellow at the University of Oxford, who studies dengue in Vietnam. As well as helping to develop new drugs and vaccines for dengue, he is researching better diagnostic and prognostic tests to help doctors make decisions about dengue, and novel approaches to vector control.

"The important point," he says, "is that all these approaches can be complementary. We're not going to eradicate the virus any time soon, so we need a swag of tools to control dengue."

It's a point that applies to NTDs as a whole: each presents specific challenges, but they all require continuing research across the spectrum from basic to applied and will need a range of strategies to control, eliminate or even eradicate them.

Grouping these diseases together under a collective name doesn't necessarily help the research effort, but it has succeeded in drawing more attention to the huge problem they continue to present and the need for sustained, coordinated action. Hotez highlights some of the achievements made since 2005, when the first paper to use the term 'neglected tropical diseases' was published: they include major initiatives from the US Agency for International Development and the UK Department for International Development; a new Department of Control of Neglected [Tropical Diseases](#) at the WHO; and PLoS NTDs, which launched in 2007.

Ultimately, says Fenwick, it will be impossible to achieve any of the Millennium Development Goals without tackling NTDs. "How can you break the poverty cycle?" he demands. "How can you achieve primary education for all if the kids are full of worms? If they have no energy so that even if they go to school they fall asleep?"

It's a persuasive argument and one that he, Hotez and others will continue to make to anyone who will listen. "I think as scientists we are taught not to be advocates," says Hotez. "That's something I'm trying to correct."

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