

STORIES OF PROGRESS:

NEGLECTED TROPICAL DISEASES, MALARIA AND TUBERCULOSIS

Thinking beyond traditional models

TRANSFORMING LIVES

PRESENT DAY ...

NISHA'S EXPERIENCE WITH LYMPHATIC FILARIASIS, A NEGLECTED TROPICAL DISEASE

Nisha receives treatment for the disease through donations received as part of the London Declaration.



TWENTY YEARS AGO ...

In 1998, Nisha might not have had access to treatment and would have lived with this debilitating disease all of her life. IN THE FUTURE..

Nisha hopes that partnerships will continue to provide access to treatment for everyone suffering from lymphatic filariasis (LF), enabling it to be eradicated globally.

NTDs, malaria, and TB carry significant social and economic burdens, despite the fact that many of these diseases can be effectively controlled, and in many cases, eliminated. Because these diseases disproportionately affect vulnerable people, mainly in LMICs, they do not receive the same level of attention as other diseases.

These diseases worsen and reinforce poverty, persisting in populations with limited access to adequate sanitation or medical care and in close contact with infectious vectors and domestic animals and livestock.

Women, children, and HIV/AIDS sufferers are most likely to be infected by NTDs. Women are particularly likely to be affected due to gendered roles which expose them to transmission, such as caring for sick children, cleaning of materials likely to carry infection, or collecting water.¹⁷⁹ The majority of malaria deaths are in children under five and one million children catch TB each year. Sick children miss out on school, illness reduces families' earnings, and diseases are a huge burden on already fragile healthcare systems.



INNOVATIVE RESEARCH MODELS

A central challenge for this group of diseases is the lack of competitive markets for vaccines and medicines in the LMICs where the diseases are most prevalent. In spite of these challenges, R&D-based biopharmaceutical companies are working to accelerate the elimination or control of these diseases through the discovery of new treatments and interventions through innovative mechanisms, including product development partnerships (PDPs), IP sharing and open innovation, and programs to expand access in endemic countries.

Companies foster R&D by sharing IP assets, compound libraries, access to research facilities, hosting scientists and providing training. Additionally, the private sector has transferred technology and built technical expertise to develop, manufacture, register and distribute products. The Tres Cantos Open Lab Foundation allows independent researchers to access GSK facilities, resources, and expertise to advance research into TB, malaria and kinetoplastid infections. Similarly, the Novartis Institute for Tropical Disease is a collaborative research centre, where academic institutions such as the University of Singapore and non-profits such as the TB Alliance work together with Novartis scientists to develop new therapies. WIPO Re:Search is a global consortium of over 100 companies, academia, research centers, non-profits and government agencies that facilitates sharing of know-how, technologies, and bridge research gaps. To date, 95 research collaborations have been established through WIPO Re:Search by BIO Ventures for Global Health.

Innovative collaborations have tremendous potential to advance progress towards new drugs and diagnostics addressing neglected diseases. 90% of NTD related programs in which IFPMA members are active are collaborative efforts which involve over 50 organizations, including universities, NGOs, and public and private sector institutes.¹⁸⁴

AN INNOVATIVE PUBLIC-PRIVATE PARTNERSHIP

The first of its kind in Japan, the Global Health Innovative Technology (GHIT) Fund, is a partnership between the BMGF, the Japanese government, pharmaceutical companies, the Wellcome Trust and UNDP.¹⁸⁵ The fund invests and manages a portfolio of development partnerships, mobilizing Japanese and international pharmaceutical companies and academic organizations to get new medicines, vaccines, and diagnostic tools to people afflicted by NTDs.

PARTNERING FOR DELIVERY

In many cases, methods to prevent, diagnose and treat these diseases are known. Much harder, yet equally essential to eradication, is ensuring access to interventions. This is where innovative partnerships are important.

Many R&D-based pharmaceutical companies have committed to drug donations until diseases are eliminated. The progress realized through these global donation efforts demonstrates the power of strategic collaboration in reducing the impact of NTDs on health and society.

Partnerships and collaborative efforts such as The London Declaration on Neglected Tropical Diseases (The London Declaration), USAID Neglected Tropical Diseases Programme, Medicines for Malaria Venture (MMV) and the Stop TB Partnership bring together public, private, and civil society actors to improve access to treatments, capacity building and policy advocacy. These are essential to end these diseases.

The success of drug distribution campaigns relies on an integrated treatment approach. In the past, many countries conducted separate treatment campaigns for individual diseases. Now, many programs provide treatments for several diseases at the same time. For example, a national program can treat all children in a region for intestinal worms, onchocerciasis and LF in a single school visit. These large-scale campaigns also offer an opportunity to reach people with other health interventions and can support country progress towards stronger health systems and UHC.¹⁸⁶





NEGLECTED TROPICAL DISEASES

KEY MILESTONES

1971: Benznidazole introduced for the treatment of Chagas disease. ¹⁸⁷

1975: Development of albendazole for treatment of parasitic worm infections including cysticercosis.¹⁸⁸

1986: Approval of clofazimine to treat leprosy, a key constituent of multidrug therapy (MDT) alongside rifampicin and dapsone.¹⁸⁹

1987: Development of ivermectin (also known as Mectizan®) for parasitic infections in animals and finds it can be used to treat river blindness in humans and LF. Established the Mectizan® Donation Programme to provide ivermectin to all who needed it, for as long as needed. ¹⁹⁰

1998: Azithromycin begins to be prevalently used as a first-line response for eliminating blinding trachoma.¹⁹¹

2003: The term 'neglected tropical diseases' is coined by Peter Hotez and colleagues to counterbalance the attention given to HIV/AIDS, TB and malaria.¹⁹²

2007: First Global Partners' Meeting on NTDs held at WHO headquarters in Geneva, bringing together over 200 public and private institutions dedicated to contributing their time, efforts, and resources to control neglected tropical diseases. ¹⁹³

2009-13: USAID launches Neglected Tropical Diseases Initiative committing USD 350 million to deliver integrated NTD treatment to 300 million people in Africa, Asia, and Latin America. ¹⁹⁴

2012: WHO NTD Roadmap sets targets and milestones to control, prevent, eliminate, and eradicate NTDs.¹⁹⁵

2012: The London Declaration on Neglected Tropical Diseases (The London Declaration): 14 billion treatments pledged and commitment to control, eliminate or eradicate 10 debilitating NTDs responsible for more than 90% of the burden by 2020. ¹⁹⁶

2013: Development of high-quality diethylcarbamazine citrate tablets for treatment of LF, with a formulation suitable for worldwide distribution.¹⁹⁷

2015: The number of people requiring treatment and care for neglected tropical diseases falls 21% since 2010, to 1.6 billion people. 198

2016: Approval of new child-friendly chewable tablet formulation for children infected by intestinal worms (soil-transmitted helminthiasis). ¹⁹⁹

2017: Clinical trial results show efficacy and safety of fexinidazole, the first oral monotherapy for Human African Trypanosomiasis, which could avoid the need for lumbar puncture and for systematic hospitalization of patients.²⁰⁰

2017: NTD Summit (Geneva): half-way to The London Declaration, which has been awarded the title of 'biggest donation' ever by Guinness World Records.²⁰¹

WHO LIST OF

NEGLECTED TROPICAL DISEASES

HELMINTH

Dracunculiasis (guinea-worm disease)

Echinococcosis

Foodborne trematodiases

Lymphatic filariasis

Onchocerciasis (river blindness)

Schistosomiasis

Soil-transmitted helminthiases

Taeniasis/Cysticercosis

BACTERIA

Buruli Ulcer

Leprosy (Hansen's disease)

Trachoma

Yaws (Endemic treponematoses)

VIRUSES

Dengue and Chikungunya Rabies

PROTOZA

Chagas Disease

Human African trypanosomiasis (sleeping sickness)

UPDATED 2017

Leishmaniasis

ADDED IN 2017

Mycetoma, chromoblastomycosis and other deep mycoses

Scabies and other ectoparasites
Snakebite envenoming

THE BREAKTHROUGH
GLOBAL COLLABORATIVE
EFFORT TO CONTROL
RIVER BLINDNESS
RESPONDED TO THE
LINKS BETWEEN
DISEASE AND RURAL
DEVELOPMENT AND
FOR THE FIRST TIME
RECOGNIZED HEALTH AS
AN INVESTMENT WITH A
POSITIVE RETURN.

Tim Evans, World Bank Group One in seven people suffer from an NTD, ²⁰² with the vast majority of cases in LMICs where parasites, bacteria and viruses thrive in subtropical climates. NTDs are painful and can blind, disfigure, and cause severe and permanent disabilities. Disfiguring NTDs such as Buruli ulcer, yaws, and leprosy are frequently associated with stigma, increasing the burden of disease.

Progress has been made in eradicating NTDs with the elimination of some diseases in certain geographies. A notable milestone was the discovery that ivermectin for parasitic infections could be used to treat river blindness and lymphatic filariasis (LF) in humans. There was no market as those infected were too poor to pay, so MSD made an open-ended commitment to give away as much of the drug as necessary until river blindness is eliminated.²⁰³ Similar commitments followed. In 2017 the Japanese pharmaceutical company Eisai renewed its pledge to donate diethylcarbamazine until the global elimination of LF is achieved.²⁰⁴ GSK has donated eight billion tablets of albendazole to date to prevent LF and control intestinal worms and has also pledged to donate albendazole to every country that needs it until LF is eliminated. Lymphatic filariasis transmission has now been eliminated in 11 countries including China, Costa Rica, Egypt, South Korea, Sri Lanka, and Thailand.²⁰⁵

The Drugs for Neglected Diseases Initiative (DNDi) works in partnership with industry, research institutions and the public sector on the most neglected diseases. This includes Human African Trypanosomiasis (HAT), leishmaniosis and Chagas disease, which fall outside the scope of market-driven R&D.²⁰⁶ USAID Neglected Tropical Diseases Programme delivers integrated NTD treatment to 300 million people in Africa, Asia and Latin America and reached two billion treatments by 2016.²⁰⁷



In addition to the donations by MSD, GSK and Eisai, a number of other programs focus on the elimination of particular NTDs:

- → Bayer works with WHO to tackle Chagas disease and African Sleeping Sickness, both of which are completely curable in the early stages with drugs.²⁰⁸
- → **Pfizer** partners with the International Trachoma Initiative an independent NGO dedicated to eliminating trachoma to donate antibiotics and work with agencies to implement the WHO recommended SAFE (Surgery, Antibiotics, Facial Cleanliness, and Environmental improvements) strategy for trachoma control.²⁰⁹
- → Merck KGaA works to fight schistosomiasis in Africa through its 'One Merck for Schistosomiasis' program, which includes the development of a pediatric formulation of praziquantel via a consortium of partners to treat children younger than 6 years old and the development of innovative schistosomiasis diagnostics in association with the current efforts of the BMGE.²¹⁰
- → **Johnson & Johnson** co-founded Children Without Worms to tackle soil-transmitted helminthiases through interventions including mass drug treatment and preventative chemotherapy.²¹¹
- → **Sanofi** has initiated partnerships to address HAT including with the WHO to donate existing drugs and with DNDi to develop a new oral treatment.
- → **Novartis**, through partnering with WHO, has committed to deliver Multi Drug Therapy for leprosy to 1.3 million people by 2020.²¹²

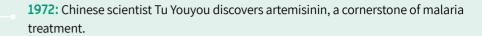
More and more countries are eliminating these diseases. River blindness and Chagas disease have been eliminated from several countries in the Americas.²¹³ Morocco, Cambodia and the Lao People's Democratic Republic have eliminated trachoma as a public health problem.²¹⁴ In 2015, India was the first country to be declared yaws-free.²¹⁵

Progress has been enabled by the large-scale donation of medicines. In 2015, nearly a billion people received donated treatments for at least one NTD. ²¹⁶ The London Declaration is a flagship partnership for driving control or elimination of NTDs. The industry is delivering on its promise of 14 billion donated treatments (USD 7 billion worth of medicine) over 10 years. Millions of health workers and community volunteers have been trained, strengthening health systems in the poorest communities to ensure appropriate treatment and care. The London Declaration has been awarded the title of 'biggest donation' ever by Guinness World Records (April 2017). By 2020, nearly USD 18 billion worth of medicines will have been distributed, the largest medicine donation the world has ever seen.

Preventative chemotherapy is one of the interventions deployed by the WHO, involving administering six medicines in seven different combinations, to combat at least five NTDs. Since the integrated approach began in 2008, 14 previously endemic countries have been declared free of at least one NTD that is receptive to preventive chemotherapy.²¹⁷

MALARIA

KEY MILESTONES



1979: Clinical trials of artemisinin published.²¹⁸

1985: First large-scale trials of insecticide treated nets.²¹⁹

1992: The RTS,S malaria vaccine enters clinical trials.²²⁰

1998: Launch of the Roll Back Malaria Partnership.²²¹

1999: The Medicines for Malaria Venture launched to develop antimalarials for the most vulnerable populations.²²²

2000: The UN General Assembly adopts the MDGs, setting a target to halt and begin reversing malaria incidence by 2015.²²³

2001: The first artemisinin-based combination therapy (ACT) is brought to the global market.²²⁴

2002: Launch of The Global Fund, the world's largest financier of anti-AIDS, TB, and malaria programs.²²⁵

2008: Launch of Global Malaria Action Plan, the first comprehensive blueprint for global malaria control and elimination.²²⁶

2009: Launch of the first high-quality ACT formulated especially for children.²²⁷

2015: The RTS,S vaccine is the first malaria vaccine candidate to receive positive scientific opinion from the European Medicines Agency (EMA).²²⁸

2015: WHO reports that since 2010, 60 countries have reported mosquito resistance to at least one insecticide class and of these, 50 reported resistance to two or more insecticide classes.²²⁹

2017: Regulatory application submitted for tafenoquine, the first new medicine for the radical cure (prevention of relapse) of *P vivax* malaria in patients aged 16 and older in more than 60 years.²³⁰

2018: RTS,S vaccine introduced in pilot immunization programs in three African countries – Kenya, Malawi, and Ghana.²³¹



Bill Gates,
Bill and Melinda Gates Foundation²⁴¹

Malaria is caused by parasites transmitted from the bites of infected mosquitoes. Malaria costs the African economy more than USD 12 billion every year. ²³² In countries with high malaria rates, economic growth is slowed by 1.3%. ²³³ Malaria control is increasingly recognized as an important tool for poverty reduction - households in Africa lose up to 25% of their income to the disease.

Between 2000 and 2015, the rate of new cases of malaria fell by 37% globally.²³⁴ Since 2000, eight countries have eliminated malaria and many others have reduced transmission to low levels.²³⁵ However, malaria remains one of the world's biggest killers.

Treatments have helped reduce malaria deaths. The current WHO-recommended first-line treatment for malaria, artemisinin, was discovered in in 1972 by Tu Youyou, a Chinese scientist who was awarded a Nobel Prize in 2015 for her discovery. Artemisinin is particularly effective when combined with other medicines in artemisinin-based combination therapy (ACT), which the standard treatment for malaria today. Novartis started producing it in the late 1990s and began marketing it in the 2000s. Alongside the discovery of novel treatments, continuous investment in R&D is needed for new pediatric formulations given that children and pregnant women are most at risk of contracting malaria. In 2009, Novartis, in partnership with The Medicines for Malaria Venture (MMV), launched the first dispersible ACT formulated for babies and children.²³⁶ New drugs to treat and prevent malaria in children are in development by the likes of Merck KGaA, who leverage the screening of compound libraries to identify new candidates.²³⁷

MMV is one of the most well-known PDPs, launched in 1999 to develop antimalarials for vulnerable populations. In 2008, MMV in partnership with Sanofi and DNDi, launched the first anti-malarial drug resulting from a public-private partnership: a fixed-dose combination of artesunate and amodiaquine which enables better adherence to treatment and reduces the risk of resistance by avoiding selective use of a specific component. MMV also works with GSK to develop tafenoquine to cure relapsing P. vivax malaria, submitted for regulatory approval in both the US and Australia in 2017. If approved, tafenoquine would be the first new medicine for the prevention of relapse of *P vivax* malaria in more than 60 years. ²³⁹

Control of malaria will be significantly aided by the development of a vaccine. After more than 30 years of research, GSK, along with partners Programme for Appropriate Technology in Health, Malaria Vaccine Initiative and the BMGF, is close to bringing a vaccine to endemic countries. RTS,S is the first, and to date, only vaccine to show partial protection against malaria among young children. The vaccine is being made available from 2018 through routine immunization programs to young children in Ghana, Kenya and Malawi.²⁴⁰

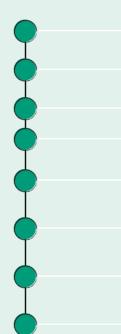
The industry recognizes that the elimination of malaria requires action in a number of different areas, not just treatments and vaccines but increasing access to antimalarials, equipping hospitals, supporting improved sanitation, training of health workers, and the strengthening of health systems. Ensuring access to vector control tools such as bed nets is fundamental to reducing cases of malaria. RBM is a global platform for coordinated

action, with 500 members including the private sector, NGOs, community organizations, foundations, and research institutions. So far 70 campaigns distributed free treated bednets to all households in areas with malaria since 2000.

The disease does not stand still. Antimalarial resistance is a real and growing threat to hard won progress. For the first time in 10 years, global malaria cases are no longer falling, driven in part by drug resistance. ²⁴² New funding mechanisms and tools such as advanced mosquito surveillance using genetic sequencing will be needed to ensure the world does not see a resurgence of the disease.

TUBERCULOSIS

KEY MILESTONES



1970: First outbreak of drug-resistant TB in the US.

1993: WHO declares TB 'a global emergency' with deaths from TB higher than any previous year.

2002: Launch of Global Fund to fight HIV/AIDS, TB, and Malaria.

2005: The number of deaths annually from TB peaks worldwide at 2 million.

2010: Launch of the Gene Xpert molecular test for TB,²⁴³ a rapid test which is endorsed by WHO and hailed as a major breakthrough.

2012: The first approval of a TB drug in 40 years, bedaquiline, unique in that it interferes with the enzyme required by bacteria to replicate.²⁴⁴

2014: Approval of delamanid, for active multidrug resistant TB, which is added to the WHO's essential medicines list.²⁴⁵

2015: WHO launches the 'End TB' strategy with the goal of ending the TB epidemic by 2035.²⁴⁶

2018: (March) Delhi TB Summit; (September) First ever UN High-level meeting on TB in New York City.

Although TB has long been preventable and curable. it is the ninth leading cause of death worldwide and the biggest infectious killer, above HIV.²⁴⁷ In 2015, 10.4 million cases (one million children) and 1.8 million deaths (170,000 children, not including those with HIV) occurred from TB.²⁴⁸ LICs and LMICs see 95% of TB deaths.²⁴⁹

An estimated 53 million lives have been saved through TB diagnosis and treatment between 2000 and 2016.²⁵⁰ Drugs included in first-line TB treatments were developed more than 30 years ago. Current treatments for multi-drug TB require patients to take multiple antibiotics for nine to 24 months or longer, are complicated to administer, and have significant adverse effects. Many patients stop their drugs before the bacteria have been destroyed, which can further encourage drug resistance. Shortening treatment regimens is a priority.

The inadequacy of current diagnosis has challenged efforts to contain the spread of TB and forms a core component of the WHO's End TB strategy. Janssen, a company of Johnson & Johnson, has partnered with the non-profit FIND to increase access to molecular diagnostics tools for TB case detection and multi-drug resistant TB (MDR-TB) diagnosis.²⁵¹

Drug resistance is another growing threat. Each year, there are roughly half a million new cases of MDR-TB, many of them transmissible. Breakthroughs by Johnson & Johnson and Otsuka have recently emerged: two new medicines (bedaquiline and delamanid) have been approved for the treatment of MDR-TB under programmatic conditions in numerous countries, with both added to the WHO's Essential Medicines List. A priority is getting these new treatments to patients by broadening sustainable and responsible access.

PRE-COMPETITIVE COLLABORATION

The **TB Drug Accelerator** is an effective example of pre-competitive collaboration and resource sharing, through which the expertise of partner organizations is leveraged to speed the development of medicines. The TB Drug Accelerator, launched in August 2012, is a BMGF sponsored discovery consortium of nine pharmaceutical companies (GSK, AbbVie, AstraZeneca, Bayer, Eisai, Eli Lilly, MSD, Sanofi, and J&J) and major academic organizations to speed up discovery and development of novel compounds against TB. Through early-stage TB research collaboration, it aims to develop five new pre-clinical drug candidates with treatment-shortening potential within five years, and proof-of-concept for a one-month three-drug regimen within 10 years. Members have opened up access to TB compound libraries to enable collaborative screening and data sharing. The TB Drug Accelerator aligns asset progression across portfolios so that members work to accelerate the most deserving discovery programs, regardless of where the drug originated, to avoid duplication. Coordinating previously siloed research teams and sharing knowledge of fundamental biology, screening capability and drug discovery resources has led to faster development timelines.

Other resource sharing programs include Eli Lilly's technology transfer program, which began in 2003 to provide R&D-based pharmaceutical manufacturers in MDR-TB 'hot spots' (China, India, Russia and South Africa) with trademarks, technology and know-how. ²⁵² The BIO Ventures for Global Health partnership hub which brokered discussions between the Centre for World Health & Medicine (CHWM) and GSK, both work on methionine aminopeptidases (MetAP) as a drug target for TB. GSK tests identifying inhibitors of MetAP had disappointed and CWHM consequently placed its MetAP inhibitor on hold to avoid repeating experiments, saving money and time. ²⁵³ The PreDICT-TB Consortium, a public-private consortium, is working to overcome the barrier of inaccurate prediction of clinical effectiveness by currently available laboratory methods in order to speed up the identification of the most effective combination of new drugs.

THE PATH TO ERADICATION

THERE A NUMBER
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Dirk Engels,
Director of Neglected Tropical
Diseases, WHO²⁵⁸

Despite progress, much remains to be done to meet SDG target 3.3 to end epidemics of TB, malaria and NTDs by 2030. The challenge consists of two missions: delivering health services for prevention and those living with diseases and eliminating transmission by addressing resistance and vaccine development.

Neglected diseases thrive in areas that lack adequate sanitation. About 2.4 billion people do not have access to adequate washing facilities. Hygiene can reduce transmission of the bacterial infection that causes trachoma. Breeding sites for mosquitoes are reduced through improved water management, limiting transmission of mosquito borne diseases. Protecting freshwater resources can prevent transmission of schistosomiasis. Improving access to water, sanitation, and hygiene (WASH) will be crucial to combat NTDs, as set out in the WHO's strategy in 2015.²⁵⁴

Climate change, growing megacities, and conflict present a challenge to meeting control and elimination targets. Overcrowding and poor hygiene and sanitation facilitate the spread of diseases. It is expected that climate change will increase the malaria burden in several regions of the world, particularly densely populated tropical highlands. An increase in NTD cases (including dengue fever and Chagas disease) in southern Europe is likely due to changing climate. Given the projected growth in the size of the world's population by 2030, more people will be living in areas at risk of neglected diseases, putting further strain on overstretched health systems and program budgets. War and refugee zones can increase exposure and susceptibility to infection. New approaches must deliver interventions in less time, provide flexible funding, and empower communities to administer care when external support is unavailable.

These diseases are not restricted to LMICs; many are found among the poor living in G20 nations. Estimates suggest that 12 million people in the US live with at least one poverty-related neglected or emerging disease. PTDs can only be eradicated if all in wealthier nations receive the treatment and care they need.

Comorbidity also remains a challenge. HIV patients are at greater risk of TB and malaria. The risk of death in co-infected individuals is twice that of HIV infected individuals without TB.²⁵⁶ There is a need to find new and improved treatments and interventions to tackle this joint disease burden.

Tackling sub-standard drugs and vaccines development remain critical to addressing drug resistance, given that antimalarials and antibiotics are the most commonly reported sub-standard or falsified products.²⁵⁷ These medicines are at best ineffective, and at worst, can result in death. They also contribute to AMR and drug-resistant infections and reduce patient confidence. Drug resistance presents a major challenge to eradicating TB and malaria. The need for ongoing innovation and a robust pipeline for treatment will become more urgent as strains become resistant to traditional treatments.

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