Since 2000, the R&D landscape for neglected tropical diseases (NTDs) – including the most neglected – has improved, although they continue to cause significant morbidity and mortality in endemic countries. The need for new, field-adapted treatments remains urgent and largely unmet.

3.1 | INTRODUCTION

Despite phenomenal advances in medicine over the past half-century, with many millions of lives being saved, adequate drugs are not sufficiently available for diseases afflicting the poorest, most neglected populations in low-income settings. While millions continue to die from preventable and treatable diseases, such as HIV/AIDS, malaria, and tuberculosis, those succumbing to other tropical diseases are all but forgotten.

Of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases including malaria and tuberculosis, although they account for 11.4% of the global disease burden (Figure 2). Tropical diseases such as malaria, human African trypanosomiasis (HAT), Chagas disease, leishmaniasis, lymphatic filariasis, dengue fever, and schistosomiasis continue to cause significant morbidity and mortality.

With progress made in advancing the fundamental knowledge of many tropical diseases, drug R&D for such diseases has significantly improved in early discovery phase, but has yet to lead to sufficient development of new drugs. Most drugs currently used to treat kinetoplastid diseases (human African trypanosomiasis, leishmaniasis, Chagas disease) have unacceptable toxicity, are not adapted to the settings in which they are administered, or are too expensive. Today, there are clear signs that the R&D pipeline for neglected diseases is being replenished, with estimates by the Bill and Melinda Gates Foundation showing that in 2009, PDPs were managing nearly 150 projects (including vaccines, diagnostics, and drugs) in preclinical and clinical development.

3.2 | SHORT- AND LONG-TERM NEEDS OF PATIENTS SUFFERING FROM NEGLECTED DISEASES

3.2.1 Overview

Most of the 17 neglected tropical diseases (NTDs), as defined by WHO, do have health tools available, but in certain cases they are far from being implemented. For NTDs that can be effectively diagnosed and treated with existing tools, enormous challenges remain in getting the treatments to those who need them. Furthermore, for many NTDs, the available diagnostics, treatments, and implementation strategies are suboptimal, incomplete, or inadequate to sustain elimination efforts. Consequently, substantial R&D investments are urgently needed to develop new-generation control tools as well as the strategies for their improved use and implementation.

DNDi’s R&D strategy addresses immediate patient needs in the short term, through improvement of existing treatment regimens and drug formulations. These treatments improve safety and efficacy, and can potentially reduce treatment duration and cost, as well as lowering the risk of resistance development. While these treatments form a substantial improvement with respect to their predecessors, currently they are not all fully adapted to supporting elimination programmes as they necessitate administration in specialized treatment centres (as opposed to simple oral treatments which can be administered in the most remote settings).

In the longer term, DNDi’s objective is to deliver innovative medicines by developing new chemical entities (NCEs). These should correspond to the target drug profiles that support elimination strategies, for example, for HAT and VL, and optimal case management for Chagas disease. The treatments should be safe, effective, short-course, affordable, and orally administered – ideally at the primary healthcare level in combination with a simple diagnostic tool. As such, these innovative medicines can have a much greater impact on public health in disease-endemic countries.

3.2.2 DNDi’s NTD Focus

Since its inception, DNDi has focused on the kinetoplastid (the most fatal of the vector-borne parasitic protozoan) diseases, a brief overview of which is provided below.

Human African Trypanosomiasis (HAT)
HAT, known as sleeping sickness, is caused by two sub-species of Trypanosoma parasites, which are transmitted to humans by the tsetse fly. Sleeping sickness, occurring only in sub-Saharan Africa, takes one of two forms, depending on the parasite sub-species (either T. b. gambiense or T. b. rhodesiense). In 2010, the estimated number of cases was 30,000, with over 36 African countries at risk, the seven most affected of which represent 97% of reported cases.

Sleeping sickness has two stages. The first entails bouts of fever, headaches, joint pains, and itching. The second stage, known as the neurological phase, begins when the parasite crosses the blood-brain barrier and invades the central nervous system. Without treatment, the disease is fatal.

Today, DNDi and FIND (Foundation for Innovative New Diagnostics) are developing new oral treatments and simplified diagnostic technologies, respectively, for HAT, with the objective that they be used together in primary healthcare centres (PHCs) rather than in hospitals where late stage HAT patients are currently treated. Once available, and with the support of an effective access strategy, these innovative tools will enable a substantial paradigm shift in the existing management of HAT, thus potentially contributing to sustainable elimination of the disease.

Leishmaniasis
Transmitted by the sandfly, the protozoan parasite Leishmania causes three different forms of disease, of which visceral leishmaniasis (VL) is the most severe. Leishmaniasis affects over 12 million people, with over 350 million people at risk (200 million of which for VL alone) in 98 countries.

VL is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, progressive anaemia, and is complicated by co-infection with other infectious diseases, such as HIV or malaria. Fatal if untreated, an estimated 500,000 new cases of VL occur each year. A significant proportion of clinical cases occurs in children.
DNDi and its partners are strongly focused on contributing to control and elimination strategies for VL. Long-term projects focus on **discovery and development of an easy-to-use, efficacious, oral drug**. Shorter-term projects aim at **development and implementation of monotherapy regimens and combination therapies**, as well as geographical extensions of existing treatments.

### Chagas Disease

Chagas disease occurs almost exclusively in the Americas. Chagas disease affects an estimated 8 million people, with 100 million people at risk in 21 countries across Latin America. Transmitted to humans by a triatomine insect containing the *T. cruzi* parasite, the disease is contracted through the bite of insects widely known as ‘kissing bugs’.

There are two clinical phases of the disease: acute and chronic. The latter can be divided into two stages: the chronic, asymptomatic ‘indeterminate’ stage, and the chronic symptomatic stage. In the acute phase (fatal for 2-8% of infected children), Chagas disease manifests generally as fever, malaise, facial oedema, generalized lymphadenopathy, and hepatosplenomegaly. The acute illness often spontaneously resolves in four to six weeks, at which time patients enter the chronic, asymptomatic ‘indeterminate’ phase that can last anywhere from 10 years to life. The symptomatic chronic stage of Chagas disease develops in up to 30% of infected persons and most commonly affects the heart. Death usually results from cardiac arrhythmia or congestive heart failure.

DNDi and its partners aim at developing a **safe, easy-to-use, oral drug effective for both stages of the disease**, in addition to improving existing treatments such as the paediatric dosage form of benznidazole. To complete its strategy for Chagas disease, DNDi is also evaluating **selected biomarkers, which could shorten the patient follow-up for test of cure**.

### 3.2.3 Portfolio Expansion and New ‘Mini-Portfolios’

While its core focus will remain on the most neglected diseases, notably kinetoplastids, DNDi has responded to a call by various international organizations and partners to address other urgent patient needs, notably for paediatric HIV and specific helminth infections. After in-depth needs assessments conducted by expert working groups, focusing on unmet medical needs, existing R&D opportunities, absence of actors, potential partners, and required resources, DNDi decided to extend its portfolio by addressing the two following specific unmet needs:

#### Paediatric HIV

According to the WHO, currently more than 2.5 million children under the age of 15 are living with HIV – 2.3 million of whom (92%) live in sub-Saharan Africa. Each day, more than 1,000 children are newly infected with HIV, and each day, an alarming 700 die from AIDS-related complications. In southern Africa, the epicentre of the pandemic, HIV/AIDS is the leading cause of under-five mortality, accounting for more than half of all child deaths in this age group in several of the highest prevalence countries, including South Africa (57%), Lesotho (56%), Botswana (54%), and Namibia (53%). According to UNAIDS, only 355,000 children with HIV/AIDS have access to antiretroviral therapy (ART). **Without treatment, one-third of children born with HIV will die before their first birthday; 50% will die before they turn two.**

Despite progress, access to ART in a formulation adapted for young children in low-resource settings is still lacking. DNDi will focus on opportunities for developing appropriate first-line treatments for children under the age of three.

#### Helminth Infections

Filarial diseases (onchocerciasis, lymphatic filariasis, and loiasis), caused by filarial nematode worms, have a low associated mortality rate but cause chronic diseases and life-long disabilities, in addition to their very high prevalence (128 million for lymphatic filariasis (LF); 47 million for onchocerciasis; unknown for loiasis). Onchocerciasis and LF can be controlled by mass drug administration (MDA; treatment duration up to 15 years). In Africa, effective treatment with the microfilaricidal drug ivermectin, exists. However,
people living in Loa loa co-endemic areas may be co-infected and in their case, the standard prevention treatment with ivermectin for onchocerciasis or LF can result in very severe neurological reactions, which can be fatal or debilitating. DNDi will focus on developing a macrofilaricide that could be used as an alternative preventive treatment and in case management. Additionally, a macrofilaricidal drug will reduce the number of MDA cycles needed for onchocerciasis and LF control in all areas. Opportunities for partnerships have been found in the animal health field and laboratory work on one new drug candidate has been initiated.

### 3.3 LANDSCAPE EVOLUTION FOR NEGLECTED DISEASE R&D

#### 3.3.1 Overview

Prior to 2000, there were few players in the field of the most neglected diseases. The Special Programme for Research and Training in Tropical Diseases (TDR), GlaxoSmithKline (GSK), and the Walter Reed Army Institute of Research (WRAIR) had specific project-related activities.

Awareness of the lack of effective treatments for neglected diseases began to grow during the late 1990s, and some novel approaches emerged to stimulate R&D and produce needs-adapted health tools. The first product development partnerships (PDPs) for neglected disease R&D were established in the 1990s (e.g. International AIDS Vaccine Initiative (IAVI) and Medicines for Malaria Venture (MMV)).

*During this period, market push and pull mechanisms*, which included various financial and economic incentives, were designed to encourage the R&D-based pharmaceutical industry to develop drugs for neglected diseases. ‘Push’ mechanisms, such as R&D grants, lower the costs and risks for companies’ R&D efforts; while ‘pull’ mechanisms, such as market exclusivity and patent extension, secure the profitability of the market (see Figure 3).

The past decade has seen a steady increase in resources given to global health and the development of new essential health tools. Today, several new actors, new donors, new financial mechanisms, and a new political environment have contributed to an increasingly active field of R&D for neglected diseases. However, greater investment – along with new and adapted funding mechanisms – is needed from both governments and the private sector to ensure that the efforts of the past two decades are strengthened and sustained.

#### 3.3.2 Key Actors

*Product Development Partnerships (PDPs)* seek to foster R&D and treatment access for neglected diseases by building partnerships based on existing capacity, expertise, and resources in both the public and private sectors. They fill a gap by focusing on essential health tools that would not otherwise be developed due to lack of profitable markets.

Currently, there are over 17 PDPs developing drugs, vaccines, microbicides, diagnostics, and devices. To date, they have developed and licensed 14 products to combat malaria, sleeping sickness, cholera, Japanese encephalitis, meningitis, VL, and TB in low- and middle-income countries, with many more tools in the pipeline.
The PDP model shows how crucial it is to build new collaborative business models through partnerships, alliances, and consortia amongst those whose objectives are driven by needs, not profit. The not-for-profit model demonstrates innovative ways to share knowledge and avoid duplication in research, thereby saving costs and speeding up the R&D process for the benefit of patients. In the past few years, DNDi has established synergies with other PDPs, for example, MMV, FIND, and CPDD. In 2010, DNDi and The Global Alliance for TB Drug Development (TB Alliance) signed the first-ever royalty-free license agreement between two not-for-profit drug developers, speeding up progress towards markedly improved therapies for multiple neglected diseases.

In past few years, DNDi has formalized strong relationships with several pharmaceutical and biotechnology companies committed to R&D for NTDs. These business relationships, at all stages of the R&D pipeline, include screening of compound libraries, access to compounds or chemical series with known anti-protozoal activity, clinical development, production, registration, and risk management plans. Such relationships illustrate the growing involvement of large pharmaceutical and biotechnology companies, as well as service providers and generic companies, from both high-income and emerging economies.

Many academic and public institutions are now players in the field of neglected disease R&D. For antikinetoplastid drug R&D, a number of low-income and emerging countries have dedicated resources to building R&D capacity (e.g. Farmanguinhos and the forthcoming Centre for Technological Development in Health at the Oswaldo Cruz Foundation – Brazil; Central Drug Research Institute – India; and Institut Pasteur Korea – South Korea).

3.3.3 Sustainable Financing

To support these initiatives, sustainable funding is needed. Global neglected disease R&D funding in 2009 totalled USD 3.2 billion (including malaria, tuberculosis, and HIV/AIDS), which is still largely insufficient to support development efforts. Furthermore, of this amount, only USD 162 million – slightly over 5% – was spent on kinetoplastid diseases.

Within the public sector, a few governments (UK, The Netherlands, Spain, Switzerland, and France) have made significant financial commitments to support innovation and implementation programmes for neglected diseases, despite financial crises. Interest in supporting NTDs has been indicated by other governments such as Germany and Australia, as well as by emerging economies. While such signs are hopeful, far too few governments are firmly engaged and commitments from major research funding sources such as the FP7 (EU) and NIH (USA) are inadequate to support PDP portfolio management.

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Within the group of philanthropic donors, the Bill and Melinda Gates Foundation (BMGF) covers almost 60% of total funding for PDPs, while the Wellcome Trust and the Rockefeller Foundation have also been important drivers. In particular for DNDi, Médecins Sans Frontières is a major financial supporter.

From its inception, DNDi has advocated for increased resources for innovation for neglected diseases and for new and sustainable mechanisms to ensure flexibility in management of portfolios. DNDi and other PDPs are examples of new forms of push mechanisms that have successfully attracted public and private funding.

Other new mechanisms, including the advance market commitment for pneumococcal vaccines and the US FDA’s Priority Review Voucher, have been launched recently by donor governments, but it is too soon to evaluate their impact. New incentives such as Milestone Prizes to stimulate early-stage discovery of promising compounds for neglected diseases should be developed.

While it can be said that there is a new political environment, a global framework for essential health R&D is still needed. Currently, WHO Member States are examining financing, coordination, and proposals for new and innovative sources of funding to stimulate R&D for neglected diseases through the implementation of the Global Strategy and Plan of Action (GSPA) on Public Health, Innovation and Intellectual Property adopted by the 2008 World Health Assembly. It is also vital that public leadership contribute to innovative needs-based measures such as IP management policies, to encourage needs-driven R&D, technology transfer, and strengthening of research and regulatory capacities in endemic countries.