DND*i*'s advocates for increased public responsibility and a more enabling environment for neglected disease R&D.



A Decade of R&D for Neglected Diseases

Despite Progress, 'Fatal Imbalance' Persists and a Global Framework Is Still Needed.

In December 2012 in New York, *Lives in the Balance: Delivering Medical Innovations for Neglected Patients and Populations*, an event co-organized by MSF, DND*i*, and Mount Sinai School of Medicine, brought together over 300 participants from civil society, academia, the pharmaceutical and biotechnology industry, ministries of health, and funding bodies to look at the progress and shortcomings of the last decade in medical innovations for neglected diseases. This conference took place precisely 10 years after MSF had hosted a major gathering in the same city to examine the crisis in R&D for neglected diseases, which ultimately led to the creation of DND*i* in 2003.

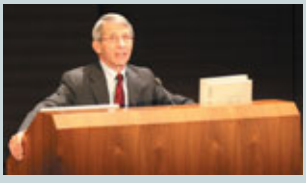
Despite incremental progress over the past decade, the essential health needs of the vast majority of the world's population are still largely unmet, current R&D efforts are still too fragmented, and financing is still far too fragile. The December conference focused on the urgent need for genuine therapeutic breakthroughs for patients dying from drug-resistant tuberculosis (DR-TB), Chagas disease, and vaccine-preventable illnesses. New therapies to fundamentally transform the treatment of these and other neglected diseases, notably those with the highest death rates, have yet to make their way through costly clinical trials and reach patients in need.

Furthering the reflections of 10 years of R&D for neglected diseases, DND*i*, MSF, and other partners undertook their own specific analysis of the R&D pipeline for neglected diseases. The study showed that while important inroads have been made, only a small fraction of new medicines developed between 2000 and 2011 were for the treatment of neglected diseases. It concluded that the 'fatal imbalance'

New York DND*i*-MSF Event (Dec. 2012): A Global Call For Action

"[T]he current model of health innovation is failing millions of the world's poorest and most vulnerable people. [W]e must work on two fronts. We need robust research and development mechanisms, producing new technologies for the diseases that afflict poor people. This means adequate, sustainable, global research investment, as well as more open approaches to sharing research knowledge. On the other hand, we must support countries to strengthen the delivery systems that will give poor people effective access to new drugs and technologies."

Dr Jim Yong Kim
President, World Bank Group

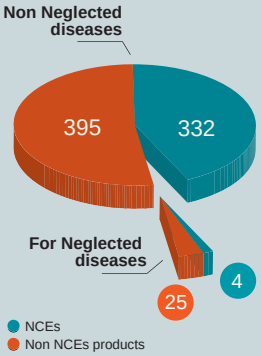


"The US is the largest public funder of neglected diseases... I say this not as a kudos to us, but as almost a challenge that we absolutely need to do more, and there's no doubt about that. And despite the constraints in resources, because it's neglected diseases doesn't mean that we should continue to neglect."

Dr Anthony S. Fauci
Director, National Institute of Allergy and Infectious Diseases, US National Institutes of Health

Progress Made but Fatal Imbalance Remains

→ **Between 2000 and 2011, only 3.8%** of newly approved drugs (excluding vaccines) were for tropical diseases, TB, and other neglected infections, which together account for 10.5% of the global disease burden.



→ **Much of the progress** in the treatment of neglected diseases and important patient benefit during this time came about through **drug reformulations** and repurposing of existing drugs against these illnesses.

→ **Only four of the 336 brand-new medicines** (new chemical entities, NCEs) developed between 2000 and 2011 were for the treatment of neglected diseases.

→ **Three of the four brand-new medicines** approved for neglected diseases in the past decade were **for malaria**, with **none for the 17 neglected tropical diseases** (NTDs) defined by the World Health Organization (WHO), nor TB.

→ As of December 2011, **only 1.4%** of a total of nearly 150,000 registered clinical trials were focused on neglected diseases.

→ **Product development partnerships (PDPs) were responsible for over 40%** of neglected disease products registered between 2000 and 2011, including new TB diagnostics and malaria combination treatments.

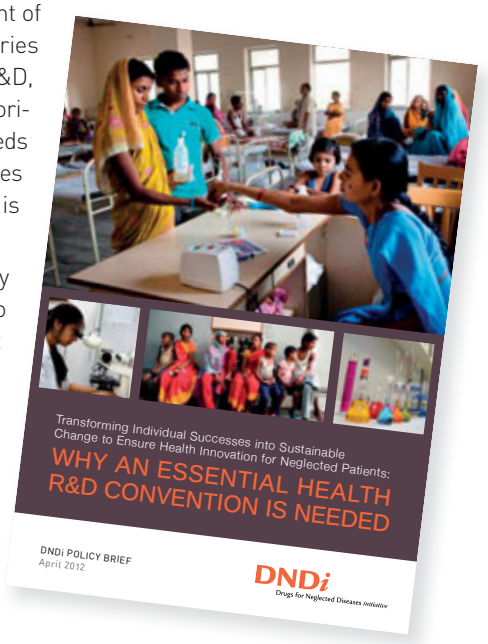
Medical innovation for neglected patients, MSF-DNDi, December 2012.

between global disease burden and drug development for some of the world's most devastating illnesses, which was the reason MSF took the first steps to found DND*i* a decade ago, was still present, despite encouraging progress made in certain areas.

The study was also prompted by the need to gain insights into neglected-disease R&D, given the 2012 recommendations of the WHO Consultative Expert Working Group (CEWG) on Research and Development: Financing and Coordination. The CEWG produced an analysis indicating that, indeed, at such a crucial time in the history of neglected diseases, it is vital to establish essential health needs-based R&D priorities and ensure that additional and sustainable financing is guaranteed. This was substantiated by a recommendation that all countries initiate formal negotiations towards a global framework that would strengthen coordination and financing of R&D and ensure that the cost of R&D be de-linked from the price of products in order to meet the needs of developing countries. In addition, the WHO's essential role in setting R&D priorities would be reinforced in the process.

DND*i* published in 2012 a policy brief, *Why an Essential Health R&D Convention Is Needed*, to relate the findings of the CEWG report to its decade of experience in drug R&D for neglected diseases. DND*i*'s 'lessons learned' included four key components:

- New financing mechanisms are necessary to provide adequate and sustainable funding, secure new funding sources, and engage public responsibility in addressing global health needs.
- R&D strategies based on open innovation models are critical to boost innovation globally, reduce duplication and costs of R&D, and speed up delivery of new medicines to patients. Such open innovation initiatives supported by public funding should be designed to secure access for patients by delinking the costs of R&D from the price of products, delivered as public goods.
- Increased involvement of disease-endemic countries in the coordination of R&D, especially in defining priorities based on patient needs and in allocating resources to identified priorities, is essential.
- Innovative regulatory pathways are needed to ensure timely patient access to treatments, reduce total costs of delivering treatments, and ultimately support greater capacity strengthening in disease-endemic countries.



DND*i* AWARDS 2013

Three Awards in 2013!

DND*i* receives prestigious awards from the BBVA Foundation, the Carlos Slim Health Institute, and the Rockefeller Foundation

In early 2013, DND*i* was honoured with the *BBVA Foundation Award for Development Cooperation* for Delivering New Treatments for Neglected Diseases with a EUR 400,000 prize. DND*i* Latin America received the 2013 *Carlos Slim Award for Innovations in Neglected Disease Drug Development* with USD 100,000 for 10 years of exceptional work in the region. In addition, DND*i* won a public voting competition for the Rockefeller Foundation's Next Century Innovators Award.

DND*i* in the news

Nearly 30 articles in mainstream media following 'Uniting to Combat NTDs' event in early 2012, and another 30 throughout the year.

Open Access to Research Results – Over 20 Scientific Publications in 2012

Neglected Diseases

More efficient ways of assessing treatments for neglected tropical diseases are required: innovative study designs, new endpoints, and markers effects by Olliaro P, Vaillant M, Sundar S, Balasegaram M. *PLoS Negl Trop Dis*, May 2012, Vol 6, Issue 5, e1545.

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Human African Trypanosomiasis (Sleeping Sickness)

Human African Trypanosomiasis in the Democratic Republic of the Congo: a looming emergency? by Hasker E, Lutumba P, Chappuis F, Kande V, Potet J, De Weggheleire A, Kambo C, Depoortere E, Pécoul B, Boelaert M. *PLoS Negl Trop Dis*, December 2012, 6(12): e1950.

In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (nect) for *T. b. gambiense* sleeping sickness by Schmid C, Kuemmerle A, Blum J, Ghabri S, Kande V, Mutombo W, Ilunga M, Lumpungu I, Mutanda S, Nganzobo P, Tete D, Mubwa N, Kisala M, Blesson S, Valverde Mordt O, *PLoS Negl Trop Dis*, November 2012, 6(11): e1920.

Identification of compounds with anti-proliferative activity against *Trypanosoma brucei brucei* strain 427 by a whole cell viability based HTS campaign by Sykes ML, Baell JB, Kaiser M, Chatelain E, Moawad SR, Ganame D, Ioset JR, Avery VM, *PLoS Negl Trop Dis*, November 2012, 6(11): e1896.

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Genotoxicity profile of fexinidazole - a drug candidate in clinical development for human African trypanomiasis (sleeping sickness) by Tweats D, Bourdin Trunz B, Torreele E. *Mutagenesis*, September 2012, 27(5):523-32.

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Liposomal amphotericin B as a treatment for human leishmaniasis by Balasegaram M, Ritmeijer K, Lima MA, Burza S, Ortiz Genovese G, Milani B, Gaspani S, Potet J, Chappuis F. *Expert Opinion on Emerging Drugs*, December 2012, Vol. 17, No. 4, Pages 493-510.

Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis by Dorlo TPC, Balasegaram M, Beijnen JH, and de Vries PJ. *Journal of Antimicrobial Chemotherapy*, July 2012.

Sodium stibogluconate (SSG) & paromomycin combination compared to SSG for visceral leishmaniasis in East Africa: a randomised controlled trial by Musa A, Khalil E, Hailu A, Olobo J, Balasegaram M, *et al. PLoS Negl Trop Dis*, 6(6): e1674. June 2012.

An image-based high-content screening assay for compounds targeting intracellular '*Leishmania donovani*' amastigotes in human macrophages by Siqueira-Neto JL, Moon S, Jang J, Yang G, Lee C, Moon HK, Chatelain E, Genovesio A, Cechetto J, Freitas-Junior LH. *PLoS Negl Trop Dis*, June 2012, 6(6): e1671.

Translational pharmacokinetics modelling and simulation for the assessment of duration of contraceptive use after treatment with miltefosine by Dorlo TPC, Balasegaram M, Lima MA, de Vries PJ, Beijnen JH, Huitema ADR. *Journal of Antimicrobial Chemotherapy*, doi: 10.1093/jac/dks164, May 10, 2012.

Visceral leishmaniasis treatment: What do we have, what do we need and how to deliver it? by Freitas-Junior LH, Chatelain E, Kim HA, Siqueira-Neto JL. *International Journal for Parasitology: Drugs and Drug Resistance*, Volume 2, January 2012.

Chagas Disease

Fexinidazole: a potential new drug candidate for Chagas disease by Bahia MT, Mayer de Andrade I, Fontes Martins TA, da Silva do Nascimento AF, de Figueiredo Diniz L, Santana Caldas I, Talvani A, Bourdin Trunz B, Torreele E, Ribeiro I, *PLoS Negl Trop Dis*, November 2012.

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Analogues of fenarimol are potent inhibitors of *Trypanosoma cruzi* and are efficacious in a murine model of Chagas disease by Keenan M, Abbott MJ, Alexander PW, Armstrong T, Best WM, Berven B, Botero A, Chaplin JH, Charman SA, Chatelain E, von Geldern TW, Kerfoot M, Khong A, Nguyen T, McManus JD, Morizzi J, Ryan E, Scandale I, Thompson RA, Wang SZ, White KL, *J. Med. Chem.*, April 2012, 55 (9), pp 4189–4204.

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Access to artemisinin-combination therapy (ACT) and other antimalarials: national policy and markets in Sierra Leone Amuasi JH, Diap G, Blay Nguah S, Karikari P, Boakye I, Jambai A, Kumba Lahai W, Louie KS, Kiechel J-R, *PLoS One*, October 2012.

Effect of the Affordable Medicines Facility – malaria (AMFm) on the availability, price, and market share of quality-assured artemisinin-based combination therapies in seven countries: a before-and-after analysis of outlet survey data by Tougher S, the ACTwatch Group, Ye Y, Amuasi JH, Diap G, *et al. The Lancet*, October 31 2012, 6(11): e1870.

Effect of artesunate-mefloquine fixed-dose combination in malaria transmission in Amazon basin communities by Santelli AC, Ribeiro I, Daher A, Boulos M, Marchesini PB, La Corte dos Santos R, Lucena MB, Magalhães I, Leon AP, Junger W, and Ladislau JL. *Malaria Journal*, 11:286, August 2012.

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Comparing changes in haematologic parameters occurring in patients included in randomized controlled trials of artesunate-amodiaquine vs single and combination treatments of uncomplicated falciparum in sub-Saharan Africa by Zwang J, Ndiaye JL, Djimde A, Dorsey G, Martensson A, Karema C, Olliaro P. *Malaria Journal*, 25 January 2012.

EUR 217 Million Secured

DND*i* experienced a successful year of fundraising in 2012, securing over EUR 33 million, up from EUR 25.8 million in 2011 (28%). This increase was directly linked to the UNITAID funding in support of the paediatric HIV mini-portfolio. Since the creation of UNITAID in 2006, this was the first time the organization allocated resources for late-stage development and treatment implementation. DND*i* also received funding from the French government and the Wellcome Trust, and additional support from the UK Department for International Development, Médecins Sans Frontières, and others.

Since its inception, DND*i* has recognized that the contribution of both public and private donors is essential to ensure the initiative's independence. Every effort is made to secure diversified funding from multiple sources and minimize earmarked donations to maintain the agility required to support research opportunities and deliver quickly.

In 2012, DND*i* made important strides in securing funding from endemic emerging economies, notably the government of Brazil. An agreement was signed with the Ministry of Health of Brazil, the Oswaldo Cruz Foundation (FIOCRUZ), and DND*i*, uniting the three actors in a strategic partnership to collaborate on R&D for new therapies and diagnostics for neglected diseases in the region.

At year-end, donors had committed over EUR 217 million, building on the EUR 184 million in 2011, since the launch of the initiative. The overall funding goal for DND*i* is to secure EUR 400 million by 2018. However, considering the financial crisis in Europe and economic constraints of a number of important donor countries, new funding mechanisms will be vital to bringing additional and sustainable resources to support DND*i* and others. Much expectation resides with the Global Health Innovation Technology Fund (GHIT Fund), set up by the government of Japan together with Japanese pharmaceutical companies and the Bill & Melinda Gates Foundation, launched in 2013. Encouragingly, the European and Developing Countries Clinical Trials Partnership (EDCTP) announced in 2012 an expansion of its scope to include all phases of clinical trials and neglected infectious diseases.

New Grants in 2012

UNITAID
USD 17.3 million (2012-2015)

This grant is to bolster development and delivery of a child-adapted antiretroviral (ARV) formulation and to begin market penetration, create a demand for the product and to promote in-country adoption. The funding will help expedite the production of 4-in-1 ARVs adapted for babies and toddlers with HIV/AIDS, including those co-infected with tuberculosis. DND*i* and partners will build on advances made in the field of paediatric HIV to date, and drive specific research and development to deliver ARV formulations that do not require refrigeration, are easy-to-administer, and are palatable, with simplified dosing.

French Government / AFD
EUR 5 million (2012-2016)

This is the third round of support DND*i* has received since 2006 from the Agence Française de Développement. This latest grant is directed toward DND*i*'s sleeping sickness portfolio activities, specifically the NECT and fexinidazole projects, as well as paediatric HIV and malaria projects.

UK Government / DFID
GBP 3.5 million (2012-2013)

The Department for International Development provided an additional grant to further implement the six treatments DND*i* delivered to date, to develop new chemical entities through high-quality clinical programmes, and to sustain discovery efforts to mitigate the risk of attrition inherent to R&D activities. Innovative drug candidates that can emanate from such efforts will play a critical role to support control or elimination strategies for leishmaniasis, sleeping sickness, Chagas disease, and filarial diseases.

Médecins Sans Frontières
EUR 3.5 million (2012-2013)

MSF's additional funding was directed toward DND*i*'s overall disease portfolio, ranging from early discovery activities to clinical trials and access. MSF's support also funded DND*i* operations to ensure the smooth running of all projects. Beyond the financial contribution, MSF provided invaluable support for clinical trials, and for expanding treatment uptake by governments, ministries of health, health systems, healthcare workers, and patients.

European Union / EDCTP (2012-2013) and FP7 Programmes
EUR 3.2 million (2012-2015)

DND*i* received two grants in 2012 from the European Union. The first came from the European & Developing Countries Clinical Trials Partnership (EDCTP) and supported malaria portfolio activities and specifically an ASMQ clinical trial project. The second came from the EU's Seventh Framework Programme, which supported the AfriCoLeish project, which aims to develop and deliver a package of care to address the needs of visceral leishmaniasis (VL) patients in East Africa. The project will test an alternative co-administration of two drugs to shorten current treatment duration, a preventive intervention for VL in HIV co-infected patients, as well as a safe and effective treatment for VL in HIV co-infected patients.

Wellcome Trust
USD 3 million (2012-2015)

This contribution enabled DND*i* to search for new biological markers to measure treatment efficacy (test of cure) for the leading parasitic killer of the Americas, Chagas disease. The three-year study is taking place in Texas, USA.

Swiss Government / SDC
CHF 0.9 million (2012-2013)

This supplemental funding was directed toward DND*i*'s malaria portfolio, which consists of running an extensive clinical trial programme in three countries in Africa, targeting children under five, to validate the efficacy and safety of the fixed-dosed combination ASMQ, and supporting the technology transfer for production of the malaria treatment to Zenufa, a Tanzanian industry partner.

Medicor Foundation
USD 0.8 million (2012-2013)

Medicor's funding was directed toward DND*i*'s visceral leishmaniasis (VL) portfolio. While SSG&PM was developed and recommended by the WHO in 2010 as a safer, effective, and less cumbersome first-line treatment for VL in East Africa, DND*i* set about developing a second alternative short-course combination therapy for VL in the region.

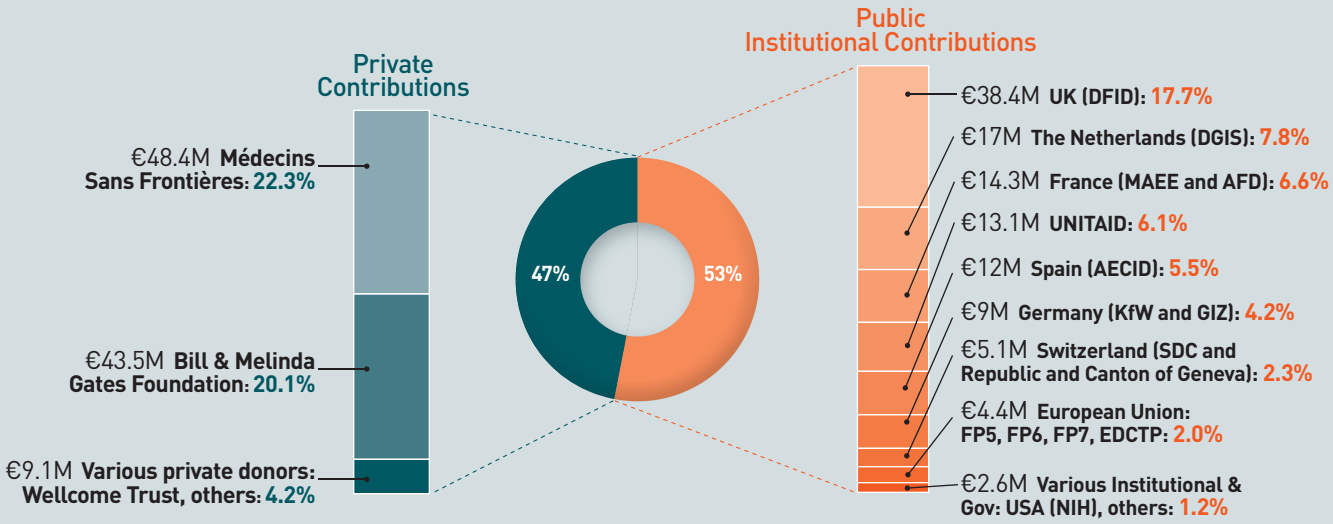
Starr International Foundation
USD 0.1 million (2012-2013)

The renewed support of the foundation to DND*i* was focused on the Chagas disease strategy in the Americas.

2012 KEY FINANCIAL PERFORMANCE INDICATORS

Maintaining balanced and diversified funding – essential to DND*i*'s vision and independence

EUR 217 MILLION COMMITTED TO DND*i* FOR 2003-2016 (AS PER DECEMBER 2012)

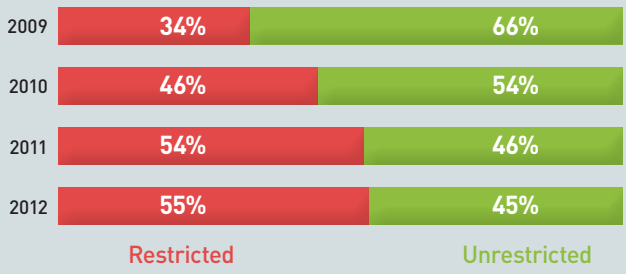


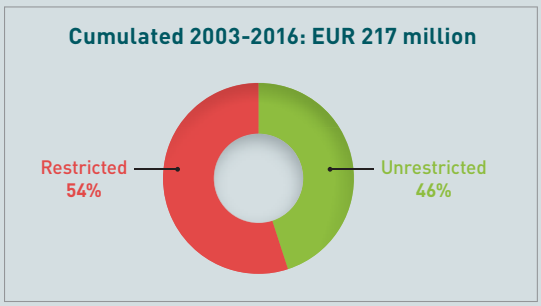
The diversification of donors increased in 2012. DND*i* welcomed additional donors including UNITAID, which pledged EUR 13.1 million toward paediatric HIV activities. To develop its activities and meet its objectives, DND*i* seeks diversified sources of funding from public and private donors, which include financial contributions from governments, public institutions, private individuals, foundations, founding partners, and innovative funding mechanisms.

Concerted efforts are made to ensure that no one donor contributes more than 25% toward DND*i*'s Business Plan, and that at maturity, half of DND*i*'s budget is covered by public funds and half by private funds. In 2012, the public-private balance was maintained as per DND*i*'s fundraising strategy. The ratio grew to 53% public support and 47% private support due to funding received from the EU Seventh Framework Programme Grant, the Agence Française de Développement, UNITAID, and the Swiss Agency for Development and Cooperation and DFID's additional contributions. New grants from private donors included the Wellcome Trust and Médecins Sans Frontières.

Challenge of a growing tendency toward restricted grants – limiting portfolio management flexibility

EVOLUTION OF RESTRICTED VERSUS UNRESTRICTED GRANTS BETWEEN 2009 AND 2012





Over the past four years, DND*i* has experienced a slight shift toward restricted funding. Ever so minimal, the percentage of grant funding is leaning toward specific diseases or R&D projects. While the ratio is still relatively balanced, greater efforts will be exerted in the coming years to recalibrate the proportion of restricted versus unrestricted funding. Unrestricted funding has been key to DND*i*'s success to date as it allowed the organization to respond quickly to research opportunities and also terminate projects that do not meet targeted goals set forth in the Business Plan. In 2012, DND*i* received significant earmarked contributions from UNITAID and the Wellcome Trust, shifting the scale to restricted funding. MSF and DFID (UK) also contributed additional funding to support core activities.

Restricted grants currently include a new category, increasingly proposed by donors: "portfolio grants". These grants are attributed to various diseases and various projects. While still restricted, they do allow for a certain degree of risk mitigation within restricted grants overall. Portfolio grants were estimated at 18% of the 2011 total income and 22% for 2012 total income.