A family in Acre, in the Legal Amazon, Brazil. Acre has been the focus of national malaria health authorities, who have found ASMQ, an antimalarial drug developed by Farmanguinhos/Fiocruz and DNDi, to be field effective in more than 17,000 patients.
In the past months, DNDi has taken key steps towards strengthening and expanding its worldwide partnerships. These partnerships enable DNDi to continue to build its robust portfolio of drug candidates targeting 3 kinetoplastid diseases (human African trypanosomiasis, visceral leishmaniasis, and Chagas disease). DNDi delivered its first products for malaria by launching ASAQ and ASMQ through innovative partnerships with private and public sectors. Both products serve today as models to foster innovation for the most neglected diseases.

Through R&D networks built on South-South and North-South collaborations, DNDi aims to bring medical innovation to patients by developing:

- New drugs from novel compounds identified through screening and lead optimisation
- New drugs from compounds with known antimicrobial/antiparasitic activities (could start at lead optimisation or pre-clinical development)
- New indications for existing medicines targeting the most neglected diseases (therapeutic switching)
- Reformulations and combinations better adapted to field conditions (paediatric, long-acting, new route of administration, fixed-dose combinations, co-packaging, or co-administration)
- Existing drugs for target diseases (geographical extension of registration to additional geographical areas, completion of regulatory dossiers of existing drug candidates).

**FACING CHALLENGES OF DEVELOPING TREATMENTS**

Over past 5 years, the R&D landscape has changed significantly, with greater attention and resources given to global health and the development of new drugs for poverty-related neglected diseases. This new landscape offers opportunities to foster innovative and successful partnerships. However, in order to achieve its mission, DNDi has to address five critical challenges.

1. **DNDi has to gain access to existing science by establishing win-win partnerships that could help build a strong portfolio.** In acting the public interest, DNDi will bridge existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners.

2. **DNDi’s primary focus is the development of new treatments for the most neglected diseases, such as sleeping sickness (human African trypanosomiasis, HAT), kala-azar (visceral leishmaniasis, VL), and Chagas disease; it will also consider engaging R&D projects on other neglected diseases. In pursuing these goals, DNDi manages R&D networks built on South-South and North-South collaborations. While using and supporting existing capacity in countries where the diseases are endemic, DNDi helps to strengthen additional capacity in a sustainable manner through technology transfer in the field of drug R&D for neglected diseases.**
3. Strengthening research capacities through technology sharing, personnel training, and infrastructure upgrading is integral to ensure sustainable innovation in endemic countries. In this respect, DNDi brought together national, regional, and international partners in order to facilitate clinical studies research in the field. The HAT Platform and Leishmaniasis East Africa Platform (LEAP), along with the Fixed-Dose Artesunate-Based Combination Therapies (FACT) Project and the Pan-Asian Network for Neglected Diseases (PAN4ND), are concrete examples of such fora. Furthermore, the clinical research platforms in Africa continuously attract more partners and allow for clinical research to be conducted in extremely difficult rural settings.

4. Innovation is pointless if it does not ultimately reach patients living in remote areas. Delivering products to neglected patients and building conditions to improve access through solid national, regional, and international partnerships remain critical.

5. Increased commitment and sustainable funding from public and private donors are prerequisites to ensure successful outcomes. In order to deliver 6 to 8 new treatments by 2014 and build a robust and well-balanced portfolio for kinetoplastid diseases, DNDi has estimated a total expenditure of EUR 275 million.

BUILDING STRONG PARTNERSHIPS

DNDi operates through a virtual model whereby all of its R&D activities are outsourced, contributing to keep development costs under control, while providing a high level of flexibility. As a consequence of this strategic option, the development of an efficient drug development programme to address neglected diseases requires the establishment of strong agreements within the entire biomedical landscape, so as to leverage and mobilise private and public sector resources. However, owing to the absence of foreseeable profit in the field of neglected diseases, these partnerships have to be built on different grounds.

> ONLY 21 NEW DRUGS IN 30 YEARS

Of the 1,556 new drugs registered between 1975 and 2004, only 21 drugs have indications for tropical diseases and tuberculosis even though these diseases constitute over 12% of the global disease burden. A mere 10% of the world’s health research expenditure is spent on diseases that account for 90% of the global burden of disease.


DNDI’S PRAGMATIC INTELLECTUAL PROPERTY (IP) POLICY

Contract terms with private and public partners are guided by DNDi’s mission to develop safe, effective, and affordable new treatments for patients suffering from neglected diseases, and to ensure equitable access.

These contracts are guided by the following principles:

• The need to ensure that drugs are affordable and access is equitable for patients who need them

• The desire to develop drugs as public goods and at cost when possible

• Primacy of the Needs of Neglected Patients, negotiating the best possible conditions for them

• Pragmatism in decisions over acquisition of patents, ownership, and licensing terms on a case-by-case basis

• Contribution to ensuring access to essential drugs and encouraging further R&D innovation.

Women and children waiting at a visceral leishmaniasis treatment centre in Ethiopia.
whereby each party obtains a tangible upside through a well-balanced agreement.

Since 2003, DNDi has demonstrated its capacity to successfully bring together academia, public health institutes, and the biotechnology and pharmaceutical industries. Since 2003, DNDi has managed 250 research, technical, and funding agreements with both public and private partners. In 2007/2008, DNDi has concluded several key agreements with the private sector and academia for the different stages of the R&D process (see Chapter 2). Successful partnership agreements require the management of divergent interests by solving critical issues like licensing rights, confidentiality concerns, intellectual property (IP) management, and/or lack of a visible profit. Defining the field (the diseases), territory (the geographical area), and the market (public vs. private distribution) are important issues that generally must be agreed upon by both parties in order for a private partner to provide DNDi access to a compound or technology.

**THE WAY FORWARD**

No single state, organisation, company, or community can meet neglected disease challenges alone. Cooperation and coordination are important elements to ensure an effective and rapid response to control these diseases. Partnership, public leadership, and increased private and public awareness are valuable in addressing urgent needs for patients suffering from these diseases. DNDi remains driven by a steadfast determination to make a difference for people affected by these diseases, in the most timely, and cost-effective way.

**MAIN PROGRESS INTO 2008**

DNDi has achieved a number of milestones since its establishment in 2003.

**Malaria**
- ASAQ - new fixed-dose combination of artesunate and amodiaquine for treatment of malaria in sub-Saharan Africa; launched in March 2007; registered in 21 countries; produced in partnership with sanofi-aventis; Good Manufacturing Practices (GMP) certification granted; WHO pre-qualification pending
- ASMQ - new fixed-dose combination of artesunate and mefloquine; successfully registered in Brazil in March 2008; produced in partnership with Farman-guinhos/Fiocruz; currently being used by Brazilian national authorities as part of ongoing intervention study (25,000 patients).

**Visceral Leishmaniasis (VL)**
- Lead Optimisation Partnership - with the aim to progress molecules proven to be safe and active in early-stage screening research, Indian partners implemented activities in 2007
- VL Combination Trial - evaluating use of approved drugs, such as miltefosine, paromomycin, and liposomal amphotericin B, began patient recruitment in May 2008 in India
- Paromomycin Trial - more than 1,000 patients included in multi-centre trial in East Africa
- Leishmaniasis East Africa Platform (LEAP) - research capacity strengthening in Africa; 5 facilities upgraded in Sudan (2), Ethiopia (2), and Uganda (1), as well as a new site has been identified in Kenya.

**Human African Trypanosomiasis (HAT)**
- Lead Optimisation Partnership - with the aim to progress molecules proven to be safe and active in early-stage screening research, American partners implemented activities in 2007
- Fexinidazole - finalising preclinical studies; intend to enter first-in-human Phase I trials in early 2009
- Clinical Trial of Nifurtimox-Eflornithine Co-Administration - promising interim safety data observed; a full dossier will be submitted to WHO in order to obtain recommendation for the use of the combination treatment in 2009
- HAT Platform - provided training on HAT patient treatment and clinical trial conduct to platform members in Angola, Democratic Republic of Congo (DRC), Republic of Congo, Uganda, and Sudan.

**Chagas Disease**
- Lead Optimisation Partnership - agreements established with partners in Australia and Brazil; focuses on progressing molecules proven to be safe and active against Chagas in early-stage screening research
- Paediatric Benznidazole - agreement established to develop formulation of benznidazole for children to be affordable and available as public goods.

It is important to remember, though, that these milestones are only part of a much longer process.

**ASAQ and ASMQ simplify treatment of malaria for children, the primary victims of malaria. A simple regimen for children and adults is as easy as 1-2-3, requiring only once-daily administration of 1 or 2 tablets, according to age, over 3 days.**
DNDi Founding Partners and Worldwide Presence

- **7 Founding Partners**
- **4 Regional Support Offices**
- **1 Affiliate**
- **2 Project Support Offices**

> THE KEY ROLE OF DNDi’S FOUNDING PARTNERS

Since DNDi’s founding in 2003, 7 key stakeholders have helped to propel the initiative. Each of DNDi’s original Board members represents one of DNDi’s Founding Partners, all of which are centres of excellence in neglected disease research and/or patient care. Drawn primarily from the public sector in neglected disease-endemic countries, they have continued to serve as the backbone of DNDi by providing their expert advice, the benefit of their experience, and key project participation.

**OSWALDO CRUZ FOUNDATION (FIOCRUZ)**

Founded in 1900, Fiocruz is the largest biomedical research institution in Latin America. Part of the Brazilian Ministry of Health, Fiocruz has facilitated health tool R&D for neglected diseases via the establishment of dedicated centres for vaccine and drug development: Biomanguinhos and Farmanguinhos. Farmanguinhos/Fiocruz, one of the largest pharmaceutical laboratories in Brazil, has a long history of drug production in the field of neglected diseases, particularly for AIDS and now with the development of the antimalarial, ASMQ (see page 25).

- [www.fiocruz.br](http://www.fiocruz.br)

**DNDi NORTH AMERICA**

Established in 2007, the affiliate of DNDi in North America supports the advocacy, fundraising, and R&D efforts of DNDi in the region. Based in New York City, USA, this affiliate operates under the direction of the DNDi North America Board of Directors and collaborates with key partners engaged in a variety of R&D activities.

- [www.dndina.org](http://www.dndina.org)

**INSTITUT PASTEUR**

Established in France in 1887, the Pasteur Institut is a non-profit private foundation dedicated to the prevention and treatment of diseases. It focuses on diseases like yellow fever, tuberculosis, poliomyelitis, hepatitis, and HIV/AIDS. With 8 Nobel Prizes awarded to its researchers, the Pasteur Institut is on the forefront of medical research with discoveries of antitoxins, BCG, sulfamides, and anti-histamines, as well as key research in molecular biology and genetic engineering.

- [www.pasteur.fr](http://www.pasteur.fr)

**DNDi LATIN AMERICA**

Opened in 2004, the DNDi Latin America regional support office is based at the Médecins Sans Frontières offices in Rio de Janeiro. With the primary aim to support regional R&D activities for Chagas disease, malaria, and VL, the Latin American office also undertakes advocacy and communications activities to increase neglected diseases awareness in the region.

- [www.dndi.org.br](http://www.dndi.org.br)

**DNDi IN THE DRC**

Since 2005, the DNDi office in the Democratic Republic of the Congo (DRC) has provided essential logistical and financial support for the nifurtimox-eflornithine clinical trial (NECT) and the HAT Platform. Based in Kinshasa, the office shares space with key project partner, the Swiss Tropical Institute.

**DNDi AFRICA**

Established in 2003, the DNDi Africa regional support office is based at the Kenya Medical Research Institute (KEMRI) in Nairobi, Kenya. DNDi Africa provides support to R&D projects in the region, including the paromomycin study, the LEAP and HAT Platforms, and the FACT Project. Additionally, the office works to build awareness about neglected diseases and realities in the field through regional advocacy and communications activities.

- [www.dndiafrica.org](http://www.dndiafrica.org)
**Vision, Mission, & Objectives**

**INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR)**

Established in 1911, it was re-designated in 1949 as the Indian Council of Medical Research (ICMR). Funded by the Government of India, ICMR’s activities are focused on the formulation, coordination, and promotion of biomedical research. The Council has a network of 21 Permanent Research Institutes located in different parts of India that conduct research on tuberculosis, leprosy, and visceral leishmaniasis.

- www.icmr.nic.in

**THE SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES (TDR)**

As an independent global programme of scientific collaboration, established in 1975 and co-sponsored by the United Nations Children’s Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO), TDR aims to help coordinate, support, and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged. TDR is a permanent observer of DNDi’s Board of Directors.

- www.who.int/tdr

**MEDECINS SANS FRONTIÈRES (MSF)**

MSF is an independent, private, medical aid organisation that has been operational in emergency medical aid missions around the world since 1971. With offices in 19 countries and ongoing activities in over 80, MSF has also run the Campaign for Access to Essential Medicines since 1999. MSF has received numerous international awards for its activities, including the Nobel Peace Prize in 1999. MSF dedicated this prize to finding long-term, sustainable solutions to the lack of essential medicines crisis (which ultimately led to the founding of DNDi in 2003).

- www.msf.org

**THE MINISTRY OF HEALTH, MALAYSIA (IMR)**

The Institut for Medical Research (IMR), within the Ministry, was established in 1900 to carry out scientific and sustained research into the causes, treatment and prevention of infectious tropical diseases. Initially, it focuses on malaria, beriberi, cholera, and dysentery. The IMR is now comprised of 8 centres which perform research, diagnostic services, training, and consultative services across diverse health fields.


**DNDi JAPAN**

Since 2004, the DNDi office in Japan has provided support in developing discovery projects and on better positioning DNDi within the country. Based in Tokyo, DNDi Japan is strengthening its presence in the country by expanding its relationships with academia, pharmaceutical companies, government, and media.

- www.dndijapan.org

**DNDi INDIA**

Opened in 2004, the regional support office in India is based at the Indian Council for Medical Research (ICMR) in New Delhi. The office functions as a relay for DNDi’s operational activities in India, which are primarily focused on two diseases, malaria and visceral leishmaniasis. R&D activities involve not only ongoing clinical trials but a number of earlier stage projects.

- www.dndiindia.org

**DNDi MALAYSIA**

Since 2004, the DNDi office in Malaysia has supported a variety of R&D activities across the Asian region, including key preclinical and early clinical studies for the FACT Project, as well as the fostering of the PAN4ND, a regional research platform that is focused on the discovery and development of natural substances as therapeutics to neglected diseases. Based at the Universiti Sains Malaysia, the office also works to facilitate the implementation of ASMQ in the region.

- www.dndiasia.org

**KENYA MEDICAL RESEARCH INSTITUTE (KEMRI)**

Established in 1979, KEMRI conducts health sciences research and shares its research findings with the international community. One of the leading health research institutions in Africa, KEMRI has and continues to make a significant contribution to regional research capacity. With a focus on infectious and parasitic diseases, and on public health and biotechnology research.

- www.kemri.org

**MINISTRY OF HEALTH, MALAYSIA (IMR)**

The Institut for Medical Research (IMR), within the Ministry, was established in 1900 to carry out scientific and sustained research into the causes, treatment and prevention of infectious tropical diseases. Initially, it focuses on malaria, beriberi, cholera, and dysentery. The IMR is now comprised of 8 centres which perform research, diagnostic services, training, and consultative services across diverse health fields.

Patient Needs and DND\textsuperscript{i} Objectives

Sleeping Sickness

Human African Trypanosomiasis (HAT)

60 million people at risk in sub-Saharan Africa

WHAT IS THE ANNUAL IMPACT OF HAT?

- 50,000-70,000 cases \textsuperscript{(1)}
- 48,000 deaths \textsuperscript{(1)}
- 1,525,000 DALYs \textsuperscript{(2)(3)}

Large proportions of communities can be affected by HAT, with serious social and economic consequences. Epidemics at the end of the 20th century infected up to 50% of population in several villages across rural Africa.

WHERE DOES HAT OCCUR?

Of the 36 countries considered endemic for HAT, the 7 most affected countries represent 97% of all reported cases [see map]. The Democratic Republic of the Congo (DRC) alone accounts for 2/3 of reported cases \textsuperscript{(4)}.

HAT primarily occurs in the poorest, most rural areas in Africa, where difficulty of diagnosis, political instability, and lack of health surveillance make estimates of disease prevalence difficult to ascertain.

HOW IS HAT TRANSMITTED?

Transmitted to humans by tsetse flies, HAT is caused by two sub-species of the kinetoplastid protozoan parasite, Trypanosoma brucei: T. b. gambiense [west African], T. b. rhodensiense [east African].

WHAT ARE THE SYMPTOMS/PRESENTATIONS?

HAT occurs in two stages:
- stage 1 - the haemolymphatic phase – includes non-specific symptoms like headaches and bouts of fever (generally goes undiagnosed without active HAT surveillance).
- stage 2 - the later, neurologic phase – occurs when the parasite crosses the blood-brain barrier (BBB) and can lead to serious sleep cycle disruptions, paralysis, progressive mental deterioration, and, ultimately, results in death without effective treatment.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Available treatments are few, old, and stage-specific. For stage 2 (where most patients are diagnosed and thus treated), 2 available treatments exist:
- melarsoprol, an arsenic derivative: painful, toxic [killing 5% of those who receive it], increasingly ineffective
- eflornithine: difficult to administer and requires trained health staff and constant hospitalisation [requiring 56 infusions of 2 hours over 14 days], and resistance an increasing concern.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?

Improved treatment options for this fatal disease are urgently needed, particularly for stage 2.
- A safe, effective, and practical stage 2 treatment would improve and simplify current case management. This drug should ideally work in both stages of disease.
- A simple stage 1 treatment, to be used at the local health centre level, would increase access to treatment and coverage.

WHAT IS DND\textsuperscript{i} DOING TO ADDRESS UNMET TREATMENT NEEDS?

DND\textsuperscript{i}’s HAT-specific portfolio balances short- and long-term objectives.

Short term: better use of existing treatments and improved research capacity
- Nifurtimox-eflornithine combination therapy (NECT), a simplified treatment for stage 2 HAT (see page 24)

Long term: new drugs and improved research capacity across region
- Fexinidazole: first drug candidate in preclinical development from nitroimidazoles project [see page 23]
- New drugs developed from compounds identified in discovery research [see pages 18-20] and progressed through HAT lead optimisation consortium [see page 21]
- Multi-country, multi-partner HAT Platform to strengthen regional research capacity [see pages 29-30]

By 2014, DND\textsuperscript{i} aims to deliver from its HAT-specific portfolio:
- 1 new combination therapy recommended by WHO
- 1 new drug registered
- A robust pipeline

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Kala-Azar
Visceral Leishmaniasis (VL)
200 million people at risk worldwide

WHAT IS LEISHMANIASIS?
Leishmaniasis is a poverty-associated disease with several different forms, of which the following are two common:
• VL: fatal without treatment
• Cutaneous leishmaniasis (CL): a spectrum of presentations; typically with self-healing or chronic lesions on the skin.
VL is the primary disease target for DNDi, whereas CL is secondary, mainly because it is not a life-threatening disease in general.

WHAT IS THE ANNUAL IMPACT OF LEISHMANIASIS?
500,000 cases of VL; 1.5 million cases of CL
51,000 deaths
2,357,000 DALYs
A lack of surveillance systems and frequency of misdiagnosis mean that it is difficult to estimate the true incidence and case-fatality rate of VL.

WHERE DOES LEISHMANIASIS OCCUR?
Leishmaniasis infects approximately 12 million people in 88 countries. VL affects poor, remote populations in 70 countries across Asia, East Africa, South America, and the Mediterranean region (see map). The 7 most affected countries – Bangladesh, Brazil, India, Ethiopia, Kenya, and Sudan – represent over 90% of new cases.

HOW IS LEISHMANIASIS TRANSMITTED?
Diversity and complexity mark the disease of leishmaniasis: more than 20 species of the kinetoplastid protozoan parasite Leishmania are transmitted to humans by ~30 species of phlebotomine sandflies.

WHAT ARE THE SYMPTOMS/PRESENTATIONS OF VL?
VL is characterised by prolonged fever, enlarged spleen & liver, substantial weight loss, and progressive anemia. These symptoms occur progressively over a period of weeks or even months.
Confection with other infectious diseases is an increasing concern: HIV-VL co-infection has been reported in 35 countries worldwide. Almost all clinically symptomatic patients die within months if untreated.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?
The number of treatments has increased in the past decade, but there are numerous drawbacks to each of the treatments, such as difficulty to administer, length to treat, toxicity, cost, and increasing parasitic resistance to treatment:
• Pentavalent antimonials: toxic & increasingly ineffective due to resistance; 30-day, hospital-based parenteral treatment
• Amphotericin B: dose-limiting toxicity; 15-20 day, hospital-based IV treatment
• Liposomal amphotericin B (AmBisome®): excellent, but expensive
• Paromomycin: registered in India, but efficacy in Africa not yet determined
• Miltefosine: first orally available drug registered in India, but expensive and teratogenic.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?
Patients need a treatment which is oral, safe, effective, low cost, and short course (≤10-day course).

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?
DNDi’s VL-specific portfolio balances short- and long-term objectives.

Short term: better use of existing treatments through geographical extension and new combinations
• Paromomycin and AmBisome®: treatments for VL not yet registered in Africa and could be used in combination with existing treatment (see page 26)
• Combination of existing therapies for VL in India: a critical step in reducing course, toxicity, and cost of treatments (see page 26)

Long term: new drugs and improved research capacity
• Buparvaquone and amphotericin B polymer: compounds which could improve upon route of and length of current treatments (see page 22)
• New drugs developed from compounds identified in discovery activities (see pages 18-20) progressed through VL lead optimisation consortium (see page 21)
• Multi-country, multi-partner LEAP to strengthen regional research capacity (see pages 29-30)

By 2014, DNDi aims to deliver from its VL-specific portfolio:
• 1 new drug registered
• 2 geographical extensions in endemic regions outside India by 2014
• 2 new co-administrations recommended by WHO
• A robust pipeline

References:
4. Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of developing countries as of 2007.
WHAT IS THE IMPACT OF CHAGAS DISEASE?
Approximately 8 million cases (1)
14,000 deaths (2)
667,000 DALYs (3)
Chronic Chagas disease results in significant disability with great social and economic impact including unemployment and decreased earning ability. In Brazil alone, losses of over US$ 1.3 billion in wages and industrial productivity were due to workers with Chagas disease (4).

WHERE DOES CHAGAS DISEASE OCCUR?
Endemic in 21 countries across Latin America, Chagas disease kills more people in the region each year than any other parasite-born disease, including malaria. Patient numbers are growing in non-endemic, developed countries (e.g. Australia, Canada, Japan, Spain, and the United States), due to increased migration of Latin American immigrants unknowingly carrying the parasite in their blood (see map).

HOW IS CHAGAS DISEASE TRANSMITTED?
Caused by the kinetoplastid protozoan parasite Trypanosoma cruzi, Chagas disease is primarily transmitted by large, blood-sucking reduviid insects widely known as “the kissing bugs” in endemic countries. Other ways of transmission are blood transfusion, organ transplantation, as well as congenital and oral transmissions.

WHAT ARE THE SYMPTOMS/PRESENTATIONS?
The disease has two clinical stages:
• Acute (in which 5% of children die) - characterised by fever, malaise, facial oedema, generalised lymphadenopathy, and hepatosplenomegaly - often spontaneously resolves in four to six weeks
• Chronic disease has two phases:
  – chronic asymptomatic “indeterminate” disease, during which patients can transmit the parasite to others while showing no signs of the disease, can last 10 years to life
  – chronic symptomatic disease develops in 10% to 30% of infected patients and most often involves the heart or gastrointestinal tract.
Chagas disease is a leading cause of infectious cardiomyopathy worldwide.

Current treatments can cure infected patients, but highest efficacy is seen early in infection.
• Benznidazole, nifurtimox to treat acute & early indeterminate disease:
  – Long treatment period (30-60 days)
  – Dose-dependent toxicity
  – High rate of patient non-compliance
  – No paediatric strengths
• No treatment for chronic disease.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?
Improved treatment options are needed for all stages of Chagas infection:
• A paediatric strength which is affordable, age-adapted, safe, and efficacious would cure patients early on in the disease.
• A new drug for chronic disease that is safe, efficacious, and adapted to the field, and ideally would work in both stages of the disease.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?
DNDi’s Chagas-specific portfolio balances short- and long-term objectives.
Short term: better use of existing treatments through new formulations, therapeutic switching, and combination therapy
• Paediatric strength of benznidazole: first treatment designed specifically for children (see page 24)
• Azoles: clinical development of a well-known compounds already used against fungal infections (see page 22)
Long term: new drugs and improved research & treatment capacity
• New drugs developed from promising compounds identified in discovery activities (such as GSK library of pyridones and cysteine protease inhibitors - see page 18) and progressed through Chagas lead optimisation consortium (see page 21)

By 2014, DNDi aims to deliver from its Chagas-specific portfolio:
• 1 new paediatric strength available
• 1 new drug registered

(3) DALY’s are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.
Malaria
3.2 billion people at risk

WHAT IS THE ANNUAL IMPACT OF MALARIA?
350 to 500 million new cases (1)
Over 1 million deaths (1)
42,280,000 DALYs (2)
Malaria is the leading parasitic cause of morbidity and mortality worldwide, especially in developing countries where it has serious economic and social costs. Malaria is thought to slow annual economic growth by 1.3% in endemic areas with high prevalence. The economic cost of malaria in Africa alone is estimated at US$12 billion every year (3).

WHERE DOES MALARIA OCCUR?
Malaria is present in over 100 countries and threatens half of the world’s population.
In sub-Saharan Africa, where it is the single largest cause of death for children under five, malaria kills one child every 30 seconds – approximately 3,000 children every day.

HOW IS MALARIA TRANSMITTED?
Transmitted from person to person by the bite of anopheline mosquitoes, malaria is caused by the Plasmodium parasite. Four species are involved: P. falciparum, P. malariae, P. vivax, and P. ovale. P. falciparum is the main cause of severe clinical malaria and death.

WHAT ARE THE SYMPTOMS/PRESENTATIONS?
Malaria begins as a flu-like illness 8 to 30 days after infection. Symptoms include fever (with or without other signs or symptoms such as headache, muscular aches and weakness, vomiting, diarrhea). Typical cycles of fever, shaking chills, and drenching sweats may then develop. Death may be due to brain damage (cerebral malaria), or damage to vital organs.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?
Effective treatments exist, but there are limitations:
• Widespread drug resistance: chloroquine, one of the easiest to use and most available malaria treatments, is no longer effective, with parasite resistance at more than 90% in some parts of the world (4)
• Existing combination therapies, now adopted as first-line treatment in most malaria-endemic countries, can be expensive and have complicated treatment regimens
• Limited access of neglected patients to the few paediatric strength, fixed-dose ACTs which are available
• The countries suffering the most from malaria lack the necessary capacity and funding to deliver the drugs to the patients who need them.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?
Patients in malaria-endemic countries need inexpensive, efficacious, and field-adapted drugs.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?
DNDi’s malaria-specific portfolio aims to facilitate the widespread availability of the two products delivered by its diverse partners in the Fixed-Dose Artesunate Combination Therapy (FACT) Project.

Because of numerous antimalarial R&D activities (eg. Medecines for Malaria Venture), DNDi is phasing out its malaria activities to focus on the kinetoplastid diseases.

The FACT Project has produced 2 fixed-dose ACTs which are:
– Easy to use as given in a single daily dose of 1 or 2 tablets for 3 days
– A 2-in-1 fixed-dose combination (FDC) of drugs that ensures both drugs are taken together and in correct proportions
– Age-based dosing to facilitate proper dosing in rural, remote areas
• ASAQ – FDC of artesunate and amodiaquine for treatment of malaria in sub-Saharan Africa; now registered in 21 countries
• ASMQ – FDC of artesunate and mefloquine registered in Brazil in March 2008 and in use by Brazilian national authorities as part of ongoing intervention study

Into 2014, DNDi will support the proper use of these FACTs along with the other effective ACTs so as to maintain the effectiveness of artemisinin as a first-line treatment.