MAKING TREATMENT SAFER AND MORE EFFECTIVE FOR PEOPLE LIVING WITH CHAGAS DISEASE

An update on DND*i*'s Chagas disease portfolio

DND*i*
Drugs for Neglected Diseases *initiative*

Photo: Fábio Nascimento/DND*i*

A disease hidden in the shadows of poverty and neglect

Fewer than 10% of people with Chagas disease in the Americas have been diagnosed and only about 1% of those with the disease have received antiparasitic treatment. If not treated, Chagas may cause irreversible, life-threatening damage to the heart and other vital organs. Current medications, discovered half a century ago, are effective during the acute and early chronic phases of the Chagas. However, they may have undesirable side effects and are not as effective once moderate to severe complications have developed in the advanced stage of the disease.

DND*i* has taken a leading role in developing safer, more effective treatments for people affected by Chagas disease. It also coordinates a Chagas Clinical Research Platform to optimize collaboration between the various international investigators working to improve the clinical arsenal against the disease. While working to develop better treatment alternatives, DND*i* is also focused on improving access to diagnosis and treatment with the existing tools. This approach not only provides an immediate way to reduce the heavy burden of the disease and improve patients' lives but helps integrate comprehensive care for Chagas disease into health systems so that, as they are developed, new diagnostic and therapeutic tools can be quickly adopted by providers and made available to patients.

Chagas disease, or American trypanosomiasis, is a neglected tropical disease (NTD) endemic in 21 countries in Latin America, but present also in North America, Europe, Japan, and Australia. It is caused by the parasite *Trypanosoma cruzi* (*T. cruzi*) and transmitted by blood-sucking triatomine insects known as "kissing bugs", which thrive in housing made of adobe, mud, thatch, and other natural materials traditionally used in rural Latin America. Although once mainly associated with rural areas, the epidemiological profile of the disease has changed in recent decades, and today two thirds of people with Chagas live in cities. Nonetheless, since it was first discovered in 1909, Chagas has primarily affected poor, vulnerable populations with limited access to healthcare. Furthermore, its long-term debilitating effects, which may prevent people from working and being economically active, perpetuate this cycle of poverty and marginalization.

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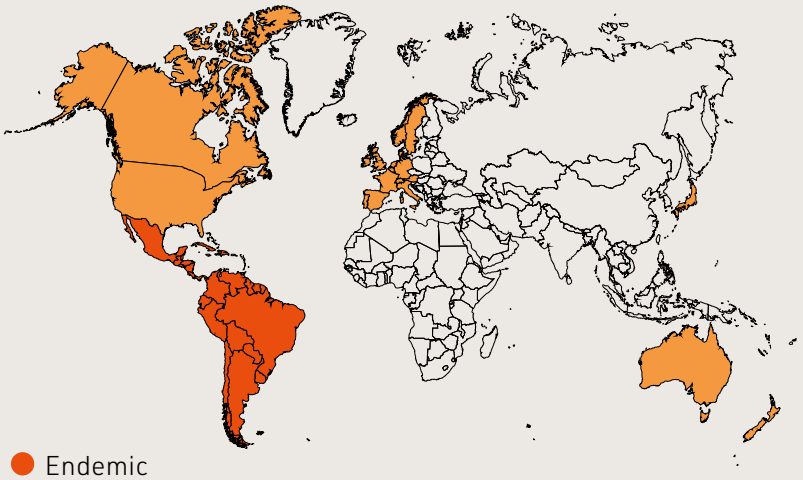
The Pan-American Health Organisation (PAHO) estimates that the disease affects approximately 6 million people, with 30,000 new cases and 14,000 deaths per year.

As the disease typically remains asymptomatic for years after infection, new cases often go unnoticed and unreported, and most people with the disease are unaware of their condition. The Pan-American Health Organisation (PAHO) estimates that the disease affects approximately 6 million people, with 30,000 new cases and 14,000 deaths per year.[1] Mother-to-child transmission is one of the main ways the disease continues to spread, with approximately 9,000 infants infected every year in the womb.

ENDEMIC IN 21 LATIN AMERICAN COUNTRIES



- Endemic
- Not endemic but present

6 million people infected in Latin America

14,000

Every year 14,000 people die

1 Pan-American Health Organization (2017). *Neglected Infectious Diseases*: Chagas Disease. Available at: https://www.paho.org/hq/dmdocuments/2017/2017-cha-chagas-factsheet-work.pdf

Chagas disease

Transmission and progression

T. Cruzi, the protozoan which causes chagas disease, is transmitted in four different ways:

1. VECTOR TRANSMISSION

The most common form of transmission is through the infected faeces of triatomines, insects popularly known by many names including "kissing bugs", "chinches", "vinchucas", or "barbeiros". These nocturnal insects live in cracks in the walls of the adobe and mud-brick houses common in rural areas in Latin America, feeding on the blood of the sleeping inhabitants. When the insect bites an exposed area of skin or mucous membranes, it defecates next to the bite. The sleeping person unintentionally scratches the bite area, allowing the parasites present in the faeces to enter the bloodstream.

The fight against Chagas has historically focused on vector control. While many countries have succeeded in interrupting vector transmission in some areas by controlling the main vectors, this remains an important form of transmission of Chagas disease. Even in areas where vectors have been controlled, transmission can reemerge if public health systems are no longer vigilant.

2. MOTHER-TO-CHILD

Mother-to-child transmission is the most significant infection route in non-endemic countries, or in those endemic countries where vector control has been successful. The paediatric formulation of benznidazole, which was developed as result of DND*i*'s collaborative work with manufacturers from Brazil and Argentina, has proved effective in treating Chagas disease in newborn babies, but only 20% of infected newborns are diagnosed. Ensuring all infants are properly tested and improving access to diagnosis and treatment for women of reproductive age are crucial steps towards eliminating Chagas as a public health problem.

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3. BLOOD TRANSFUSION OR ORGAN TRANSPLANT

Chagas can also be transmitted through non-controlled blood transfusion or organ transplant. In the past few years, there has been a significant drop in this form of transmission due to improved control in blood banks.

4. ORAL INGESTION OF CONTAMINATED FOOD

Infection is also possible through the oral ingestion of food contaminated with infected kissing bugs or their faeces. Due to the high number of parasites that enter the body at once, orally transmitted Chagas disease can be particularly severe. Oral transmission occurs mostly in the Amazon region.

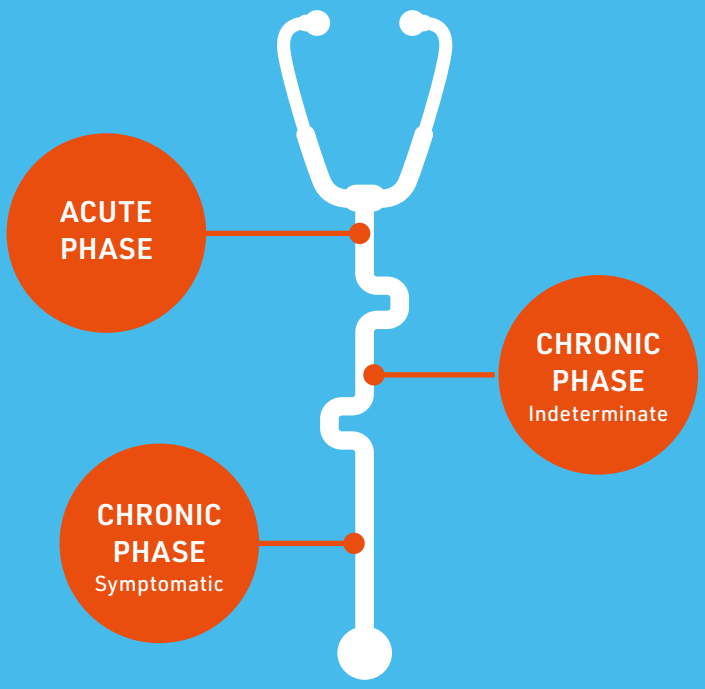
Photo: Fábio Nascimento/DND*i*

"When we started taking the drugs, I was scared because the paediatrician told us about the possible side effects."

Corina, from Bolivia, discovered she had Chagas disease just before she became pregnant. At the time, she didn't want to be treated because she didn't have any symptoms and she was worried about the side effects. Overwhelmed with guilt when her baby, Kaleb, was born with the disease, she decided to seek treatment for both Kaleb and herself, despite her concerns.

CLINICAL FORMS

Chagas disease has two clinical forms: an acute phase and a chronic phase. Most people are asymptomatic all of their lives, but roughly a third of those infected will develop an advanced chronic form with serious complications.



ACUTE PHASE

During the acute phase, which immediately follows infection, a high number of parasites circulate in the blood, but most people do not present any symptoms. When symptoms do occur, they last for about two to four months and may include rashes and inflammatory nodules, fever, headache, enlarged lymph nodes, nausea, diarrhoea and vomiting, and difficulty breathing. Occasionally, the acute phase can be fatal, especially for children. The acute phase is often easily confused with other common viral illnesses and thus goes unrecognized as Chagas disease.

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CHRONIC PHASE

After the acute phase, people infected with *T. cruzi* enter into a chronic indeterminate phase, which could last for years or decades. During this phase, parasites are still present in the body's organ tissue despite the complete absence of symptoms. People in the indeterminate phase can still transmit the disease through blood transfusion, organ transplant, or congenital transmission. For 30–40% of people infected, the disease progresses to a late chronic stage. Of these, most will suffer cardiac damage, often leading to sudden death or progressive heart failure. In a smaller number of patients, the disease causes enlargement of the gastrointestinal tract and organs and gastrointestinal motor disorders; these complications are more commonly seen in people infected in the Southern Cone of South America. Chronic Chagas disease's irreversible and debilitating symptoms may stop people from working and being economically active, which affects patients, their families and their entire communities, often perpetuating a vicious cycle of poverty.

The disease can also be reactivated in immunocompromised patients, such as people coinfected with HIV, or those receiving organ transplants or treatment for cancer. In these cases, the clinical form of the disease is severe, with high mortality rates if no treatment is provided.

Diagnosing and treating Chagas

The current scenario

There are only two drugs available to treat Chagas disease, both discovered half a century ago, underscoring a persistent lack of investment in drug R&D.

During the acute phase or during reactivation due to immunosuppression, diagnosis is generally made by direct observation via microscope of the parasite circulating in the bloodstream. During the chronic phase, when the parasite is hidden in target tissues, diagnosis is made via the detection of antibodies against *T. cruzi* through serological techniques. Because no available test is sufficiently accurate to act as a stand-alone, diagnosis of Chagas disease during the chronic phase requires the use of two or more different tests. More recently, a molecular test has been used to show the parasite DNA in the blood during acute or chronic phase, a more useful method to assess response to treatment.

There are currently only two drugs available to treat Chagas disease – nifurtimox and benznidazole – both discovered half a century ago, underscoring a persistent lack of investment in research and development for new drugs (R&D). Treatment with benznidazole, the most commonly used, lasts 60 days and may have undesirable side effects such as gastric intolerance, cutaneous rashes, or neuromuscular problems, amongst others. Nifurtimox also produces a range of side effects.

Benznidazole has proven effective in the acute and chronic indeterminate stages with around 80% of patients showing no evidence of parasites in the blood 12 months after finishing treatment. Other benefits of treatment with benznidazole include high cure rates in acute and congenital cases,


Photo: Felipe Abondano/DND*i*

and in chronically infected children, and prevention of future congenital transmission. Furthermore, it eliminates the parasite, a trigger of chronic complications, reducing or preventing life-threatening complications in adults. Finally, it treats reactivations in immunosuppressed cases.

As the disease progresses and associated complications appear, treatment effectiveness decreases, and existing protocols do not recommend treatment for patients in the late chronic stage. Yet these patients still require access to other interventions, including corrective surgeries, pacemakers, and heart transplants, as well as medications for managing cardiac or digestive symptoms.

Chagas disease

A priority for DND*i* since its founding

2003 | Since DND*i*'s inception in 2003, Chagas disease has been part of its portfolio and a priority for its research teams. At this time, benznidazole was only available in an adult-strength form, so infants and children had to be given divided or crushed tablets. With one course of treatment lasting 60 days (and two daily doses), this made it difficult for caregivers to consistently and accurately provide the right dosage.

2006 | In an expert consultation meeting led by DND*i* in October 2006, consensus was reached for the development of a paediatric formulation of benznidazole, the main drug of choice for treatment of Chagas.

2008 | DND*i* entered a partnership with the Pernambuco State Pharmaceutical Laboratory of Brazil (LAFEPE from Laboratório Farmacêutico do Estado de Pernambuco), which resulted in the development and registration of the first-ever paediatric formulation for treating Chagas disease. This was an important achievement for the 9,000 children born with Chagas every year. Non-patented, affordable, and easy-to-use, the paediatric formulation is a soluble tablet designed for infants and children up to two years of age (less than 20 kg).

2009 | The Chagas Platform was created to foster research and development for Chagas and strengthen capacity in endemic countries.

2013 | DND*i* signed a collaboration agreement with Mundo Sano Foundation and Laboratorio ELEA PHOENIX of Argentina, the only other producer of benznidazole aside from LAFEPE. The agreement aimed at securing a second source of the paediatric formulation of the drug and enabling broader registration in endemic countries to increase availability. As a result of this agreement, the drug was registered in Argentina in 2018.

Paediatric benznidazole, the first-ever formulation for treating infants and children with Chagas disease, was registered for the first time in Brazil in 2011 and added to the WHO List of Essential Medicines for Children in 2013.

2017 | As a result of a partnership with Chemo Research, its US-based pharmaceutical division Exeltis USA, and Mundo Sano Foundation, benznidazole became the first drug approved by the Food and Drug Administration (FDA) to treat Chagas disease in the US, where approximately 300,000 people are estimated to live with the disease. With this approval, the FDA granted Chemo Research a neglected tropical disease priority review voucher (PRV). The PRV is given to companies that register a qualifying drug for a rare or underserved disease; it can then be redeemed to ensure speedy review of a subsequent drug candidate or sold to another company. A substantial amount of the income resulting from the PRV sale will be used to improve registration of the drug, pricing, and to expand access to diagnosis and treatment for Chagas mainly in the Americas.

2015 | DND*i* started to work on expanding access to diagnosis and treatment of Chagas disease in Colombia. This project was later expanded to the US, Guatemala, and Brazil.

DND*i*'s strategy for Chagas disease

A three-pronged approach


Photo: Felipe Abondano/DND*i*

DND*i*'s strategy for Chagas disease consists of three pillars:

1. Improve diagnostic and therapeutic tools through innovation in R&D,
2. Foster collaboration and strengthen capacity in endemic countries through a scientific platform, and
3. Increase patients' access to diagnosis and treatment.

1. R&D: making treatment safer and more effective for people living with Chagas disease

The current challenges for Chagas treatment are threefold: tolerance, efficacy, and the lack of tools to measure response to treatment. While benznidazole is an effective treatment, for 20% of the patients the drug has not proved effective in killing the parasites. Safety and adherence to treatment is another challenge. Between 15–20% of those who start the treatment do not complete it, mostly due to undesirable side effects. DND*i*'s R&D strategy for Chagas therefore focuses on improving tolerability and efficacy of Chagas treatment as well as finding biological markers of therapeutic efficacy in patients with chronic Chagas disease.

Short-term – improve existing treatments:
In the short-term, DND*i*'s strategy for Chagas focuses on improving the treatment available by reducing patients' exposure to benznidazole, thereby increasing their tolerance to treatment while maintaining the same efficacy as the current regimen. This could be achieved by a shorter course of treatment with the same drug – currently 60 days – or a lower daily dosage. Clinical studies are being carried out to test these new regimens and, if successful, DND*i* will work with regulatory agencies to register them in key countries.

Medium term – develop new drug combinations:
Medium-term, DND*i* aims to increase efficacy of the treatment, ideally also addressing the tolerability gap. This can be achieved by reducing the dose of benznidazole and combining it with a new chemical entity known as fosravuconazole. In parallel, fexinidazole, a new drug approved in 2018 for the treatment of sleeping sickness, another trypanosomal disease, is being tested against Chagas.

Long term – develop new, more effective drugs: DND*i*'s long-term strategy involves working at the very early stages of drug discovery to find a new chemical entity that could become an effective oral treatment against Chagas disease.

Through an open collaborative model, DND*i* works with partners throughout the world on drug discovery activities for neglected diseases. The NTD Drug Discovery Booster, launched by DND*i* in 2015, is a global consortium of eight pharmaceutical companies collaborating to identify new potential treatments for neglected diseases, focusing on Chagas and leishmaniasis. The consortium uses computational approaches to screen millions of compounds from their libraries based on an active "seed" provided by DND*i*. In 2013, DND*i* launched the Lead Optimization Latin America (LOLA) consortium, DND*i*'s first early-stage research programme in countries where neglected diseases are endemic.

Also focusing on Chagas and leishmaniasis, LOLA works on "hits" that are optimized via iterative cycles of design, synthesis, biological testing and data analysis. More than 600 leads have been tested since the project was created.

DND*i* is also working on the identification and validation of a set of biological markers of parasitological cure for the disease. In addition, through the Ibero-American network NHEPACHA, DND*i* is fostering work on testing four biomarkers to assess the response to Chagas treatment. Today, the only measurable indication that someone has been cured is the disappearance of anti-Chagas antibodies, which in adults can take several decades. The identification of a suitable biomarker to show that Chagas has been cured is essential as DND*i* advances its Chagas drug development programme, to demonstrate that new drug candidates actually work.

DND*i*'S ONGOING PHASE II CLINICAL TRIALS

BENDITA

Objective: To determine the efficacy and safety of different regimens of benznidazole and benznidazole/fosravuconazole in combination to reduce and clear *T. cruzi* parasitaemia in individuals with chronic indeterminate Chagas disease.

Country: Bolivia

Number of patients: 210

Benznidazole monotherapy new regimen:
Reduced duration:
- Benznidazole 300 mg – 4 weeks
- Benznidazole 300 mg – 2 weeks

Reduced dose AND duration:
- Benznidazole 150 mg – 4 weeks

Combinations of benznidazole + fosravuconazole:
- Benznidazole 150 mg – 4 weeks + fosravuconazole 300 mg
- Benznidazole 300 mg – 8 weeks (once a week) + fosravuconazole 300 mg

Partners: Barcelona Institute for Global Health (ISGlobal), Spain; Applied Science and Studies for Health and Environmental Development (CEADES), Bolivia; National Institute of Parasitology "Dr Mario Fatala Chaben" (INP), Argentina; Institute for Research on Genetic Engineering and Molecular Biology (INGEBI), Argentina; Platform of Integral Care for Patients with Chagas Disease, Bolivia.

FEXI 12

Objective: To determine the efficacy and safety of different dosing regimens of fexinidazole in reducing and clearing *T. cruzi* parasitaemia in individuals with chronic indeterminate Chagas disease.

Country: Spain

Number of patients: 45

Tested dosages:
- Group A: Fexinidazole 600 mg for 10 days
- Group B: Fexinidazole 1200 mg for 3 days
- Group C: Fexinidazole 600 mg for 3 days, followed by fexinidazole 1200 mg for 4 days

Partners: Vall d'Hebron University Hospital, Spain; Barcelona Institute for Global Health Campus Clínic, Spain; L'Hospitalet General Hospital, Spain; University General Hospital of Valencia, Spain; La Paz University Hospital Foundation for Biomedical Research, Spain.

2. CHAGAS CLINICAL RESEARCH PLATFORM: fostering collaboration and strengthening capacity in endemic countries

In addition to development of new drugs, DND*i* focuses on strengthening research capacity in endemic countries. The Chagas Clinical Research Platform was created in 2009 and today has nearly 400 members from 150 institutions and 24 countries around the world. The platform works to catalyse the involvement of researchers and institutions from endemic countries in improving R&D for Chagas, from drug discovery to implementation. The Platform aims to enhance synergies within the Chagas clinical community to rethink patient needs and implement collaborative research that will benefit people affected by the disease.

The Chagas Clinical Research Platform was created in 2009 and today has nearly 400 members from 150 institutions and 24 countries around the world.

In 2010, the Platform played a critical role in defining a target product profile for a new Chagas disease treatment, which now guides DND*i*'s strategy and helps shape R&D efforts carried out by other researchers from the Chagas community. Platform members share a commitment to fuelling innovation, focusing on patients' needs, and providing evidence to inform public health policy and clinical practice.

The Platform also brings together a trans-regional network of clinical sites for clinical studies and implementation research, and plays an integral role in identifying emerging needs, sharing the latest knowledge, and raising awareness of new tools and practices.

Photo: Elizabeth Perez/DND*i*

Luz, 34, discovered she had Chagas disease in 2010, when her sister became ill and the doctor recommended the whole family be tested. However, when she sought treatment following her positive diagnosis, her health provider told her that treatment was only available for children.

Luz soon started to show symptoms and decided to look for alternative treatments. When she took the tests again, the results were still positive for Chagas, but this time she had good news: there was now treatment available for her.

Despite the unpleasant side effects, she decided to stick with the treatment, and even before completing the two-month regimen, she started feeling better. *"No more stinging or fatigue, everything disappeared. Recently, I took new tests and I'm currently waiting for the results."* Now Luz encourages friends and neighbours to take the test and be treated.

3. BREAKING DOWN THE BARRIERS: expanding access to diagnosis and treatment for Chagas disease

Photo: Felipe Abondano/DND*i*

Breaking down the barriers: expanding access to diagnosis and treatment for Chagas. Some of the key developments in the Chagas landscape in the past decade include the creation of the International Federation of Chagas Patients (FINDECHAGAS) in 2011, the development of the Chagas Coalition as an access champion, and the emergence of more robust evidence around treatment of chronically infected patients. However, there has been no significant change in patients' access to diagnosis and treatment, and the gap between the estimated number of people living with the disease and those who receive treatment remains abysmal. The lack of awareness of the disease, both from the general public and health professionals, coupled with widespread misunderstanding about the safety and efficacy of the existing treatment are just some of the obstacles that stop patients from being diagnosed and treated.

In 2015, DND*i* launched an initiative to increase access to diagnosis and treatment to Chagas disease in several endemic countries in the region. The objective is to demonstrate the feasibility of scaling up access to diagnosis and treatment in pilot countries with diverse epidemiological profiles, creating successful models which can then be implemented on a larger scale. To ensure pilot projects are adapted to each context, the access initiative has a four-step process which is developed and implemented in close collaboration with regional, national and local partners. This approach was first implemented in Colombia in collaboration with the Ministry of Health and Social Protection. The positive experience and promising results of the Colombia project led to the development of a collaborative project in the U.S. focused on advancing public health research on Chagas disease, including the first large-scale prevalence study in a major U.S. city in 2017. In 2018, new pilot projects were launched in Guatemala and Brazil.

The gap between the number of people living with the disease and the number receiving treatment remains abysmal.

The United States has the sixth largest global burden of Chagas disease, with more than 300,000 people affected. It also has one of the worst situations of neglect, despite its advanced healthcare system. Less than one percent of *T. cruzi*-positive people have been diagnosed or treated, and few healthcare providers are familiar with how to treat the disease. The majority of those infected are Latin American immigrants, a group which faces severe challenges to accessing healthcare.

DND*i* helped achieve a major breakthrough in 2017, when the Chemo Group's registration of benznidazole was approved by the U.S. Food and Drug Administration (FDA). DND*i* has also supported the ongoing research of the country's main provider, the Center of Excellence for Chagas Disease at Olive View-UCLA Medical Center, or CECD, in Los Angeles. The CECD's research has focused on identifying barriers, needs, and solutions for people affected by Chagas disease in the U.S., while providing screening and treatment to patients in the Los Angeles area.

The United States has the sixth largest global burden of Chagas disease, with more than 300,000 people affected.

Photo: Angela Boatwright/DND*i*

Colombia

Strengthening patient care in endemic settings

Despite an estimate of 5 million people at risk of Chagas disease in Colombia, only 1.2% were screened for the disease. Because of a cumbersome diagnostic process, people who screened positive sometimes had to wait over a year for confirmatory test results, and a third of those screened never received the confirmatory test at all. This represented an enormous barrier to starting treatment.

DND*i* partnered with the Ministry of Health to launch a Chagas treatment access pilot project, where DND*i*'s role was to catalyse a public health response to Chagas by providing technical consultation and organizational support for the creation and implementation of a new patient-centred roadmap that greatly simplified the diagnostic process and moved treatment into more accessible primary care facilities. In the pilot project, the patient-centred roadmap was implemented in five Colombian communities where Chagas disease is endemic.

Despite an estimate of 5 million people at risk of Chagas disease in Colombia, only 1.2% were screened for the disease.

DND*i* played a coordinating role and provided training for medical staff while strengthening local epidemiological surveillance. As part of the project, DND*i* also developed information, education, and communication campaigns to raise awareness of Chagas disease in the general public as well as among health care personnel.

Preliminary results from the pilot communities show a nearly 1000% increase in the number of people screened, while average wait times for confirmatory test results have shrunk from more than one year to less than two weeks. In addition to having an important impact on the lives of those affected by the disease, the programme has also demonstrated that elements of DND*i*'s collaborative model that work well for R&D can also work for overcoming access barriers. The programme also showed that it is possible to provide sustainable, comprehensive care in an endemic setting with a low external investment.

ELIMINATING CHAGAS AS A PUBLIC HEALTH PROBLEM

To move towards eliminating Chagas as a public health problem, public health authorities in endemic countries must commit to developing and implementing guidelines that ensure diagnosis and treatment are provided at the primary healthcare level, where patients typically seek care. For patients in the chronic stage of the disease, comprehensive care is needed to manage severe associated complications. In addition, strong coordination between surveillance, prevention, primary care, and specialty care is critical to ensuring an effective public health response to Chagas.

Consistent notification of chronic cases will help determine the real burden of the disease so appropriate public health strategies can be implemented.

Most importantly, the grim toll Chagas and other neglected diseases exact on individuals, families, communities, and societies will not end until we assert and safeguard the right of all people, even the most vulnerable, to appropriate healthcare.

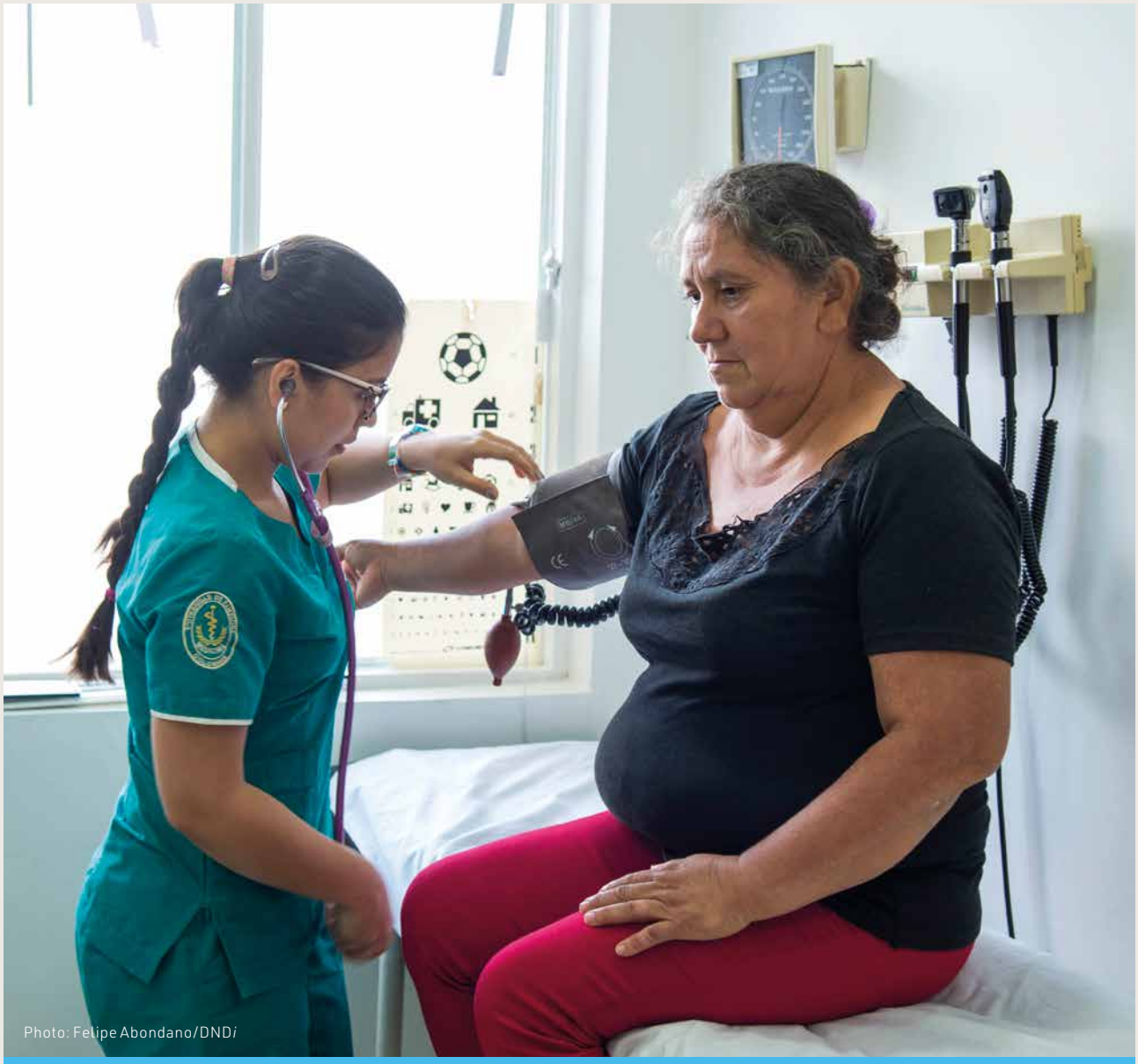

Photo: Felipe Abondano/DND*i*

“In the first 10 days, everything was normal. I only had some trouble sleeping. Then, I felt a little dizzy, had nausea, and stomach ache. I prayed to God and made a tea, and it helped me. I only feel a little dizzy now. It’s so easy to take the test now. We want to deal with this disease, that's why we're here.”

Tilcia is 52 years old and lives in Colombia. She and two of her siblings have Chagas disease. Tilcia was diagnosed after donating blood in 2014. Before starting treatment, she had to take several additional tests. Eventually, she got tired of the extensive testing and waiting for results, and she stopped going back to the clinic.

A few years later, during a health campaign in her neighbourhood, she was advised to return to the health centre. She told the doctor her story and took another test, but this time her test results took only 20 days and she started treatment for Chagas disease.

DNDi
Drugs for Neglected Diseases *initiative*

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A not-for-profit research and development organization, DND*i* works to deliver new treatments for neglected diseases, notably leishmaniasis, human African trypanosomiasis, Chagas disease, specific filarial infections, and mycetoma, and for neglected patients, particularly those living with paediatric HIV and hepatitis C.

Since its inception in 2003, DND*i* has delivered eight treatments: two fixed-dose antimalarials (ASAQ and ASMQ), nifurtimox-eflornithine combination therapy (NECT) for late-stage sleeping sickness, sodium stibogluconate and paromomycin (SSG&PM) combination therapy for visceral leishmaniasis in Africa, a set of combination therapies for visceral leishmaniasis in Asia, paediatric dosage forms of benznidazole for Chagas disease, a 'super-booster' therapy for children co-infected with HIV and TB , and the first all-oral drug for sleeping sickness (fexinidazole).

Thank you to our Chagas program donors:

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