

# Best Science for the Most Neglected

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HAT-r-ACC Project Coordinator

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*HNN 2.0 Training "International  
Cooperation and L&F issues in SC1"  
(Warsaw, PL)*



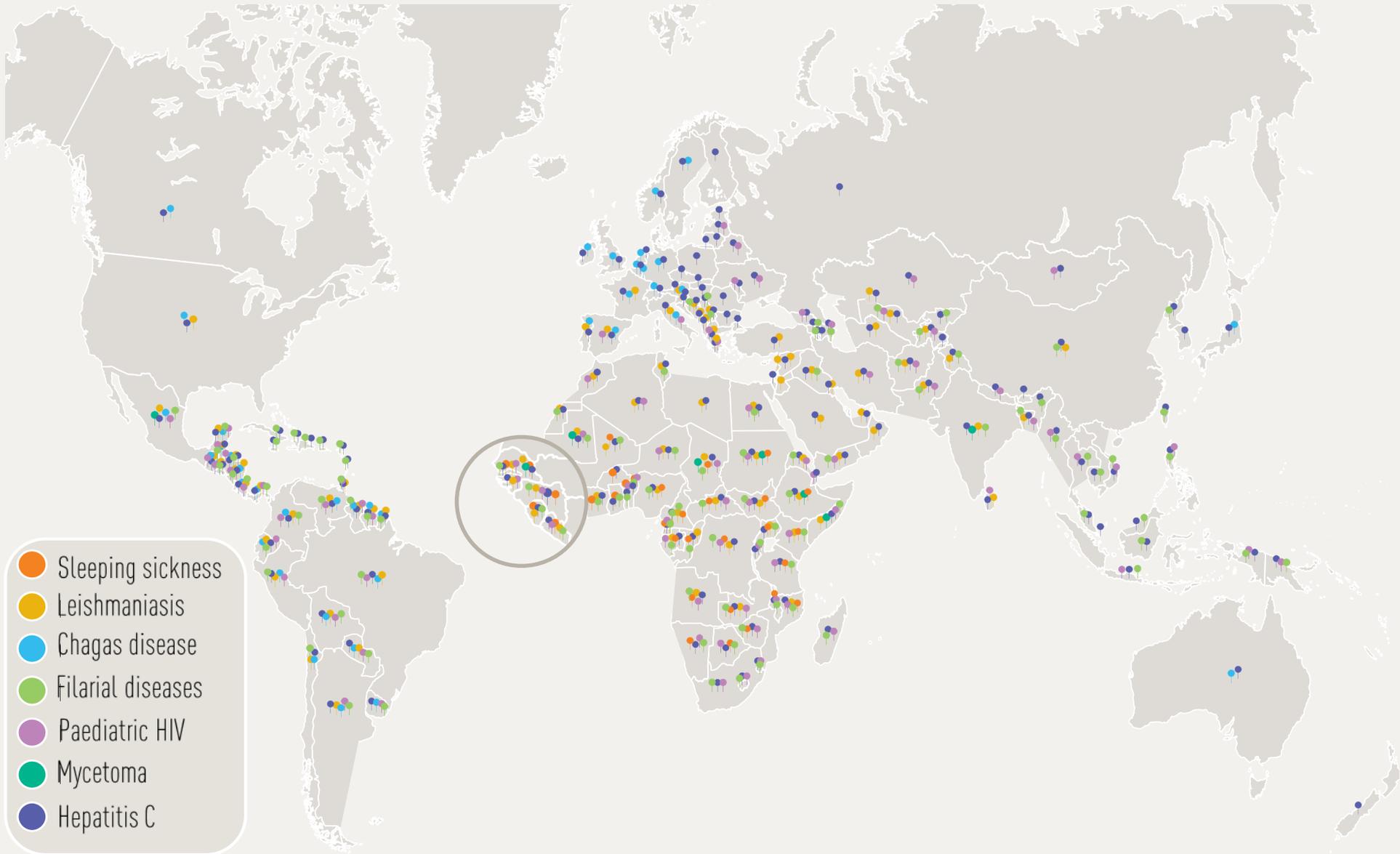
# Summary

- Neglected diseases
- The PDP model
- DNDi
- Human African trypanosomiasis
- DNDi in HAT
- HAT-r-ACC
- R-HAT
- DNDi-FEX-07-HAT

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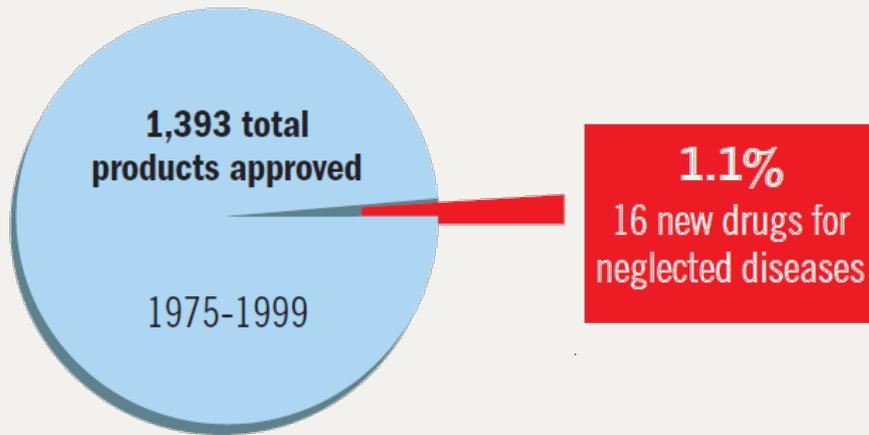
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# Neglected diseases affect patients worldwide

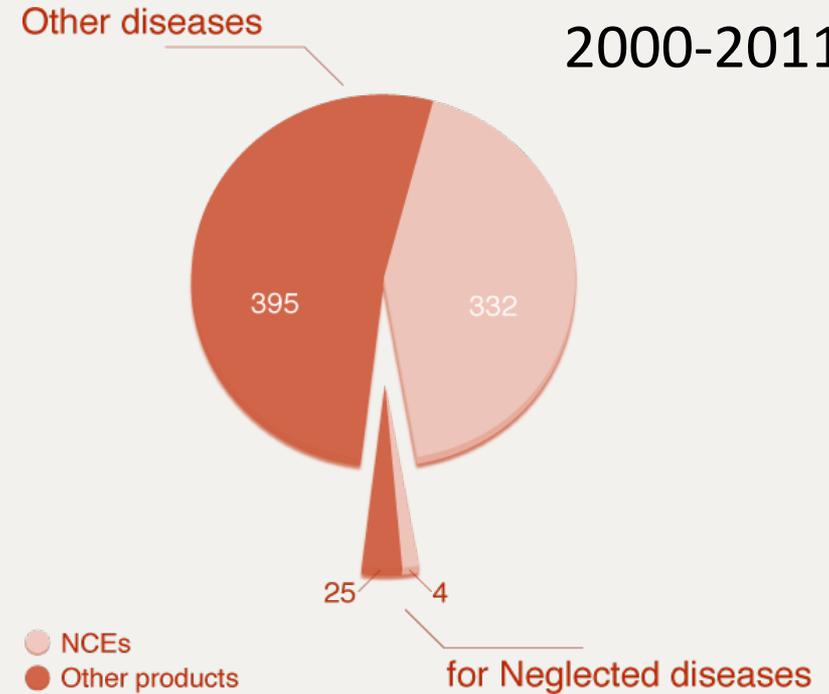


# Persistence of the fatal imbalance

1975-1999



2000-2011



- **1.1%** of new products for NTDs, malaria and TB
- But **12%** of global disease burden

- 756 products registered (excluding vaccines & biologicals)
- **1%** of 336 new chemical entities approved for NTDs, malaria and TB
- **1%** of 148,445 clinical trials registered for neglected diseases

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# New models to fill the gap in R&D for neglected diseases: Product Development Partnerships (PDPs)

Current PDP landscape working areas include:

- Vaccine R&D
- Diagnostics R&D
- R&D for new or improved treatments



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# Origins of DNDi

## 1999

- First meeting to describe the lack of R&D for neglected diseases
- MSF commits the Nobel Peace Prize money to the Drugs for Neglected Diseases Working Group
- JAMA article: 'Access to essential drugs in poor countries - A Lost Battle?'

## July 2003

- Creation of DNDi
- Founding partners:
  - *Institut Pasteur, France*
  - *Indian Council of Medical Research, India*
  - *Kenya Medical Research Institute, Kenya*
  - *Médecins Sans Frontières*
  - *Ministry of Health, Malaysia*
  - *Oswaldo Cruz Foundation/Fiocruz, Brazil*
  - *WHO –TDR (Special Programme for Research and Training in Tropical Diseases) as a permanent observer*



# DNDi's mission

- To develop new drugs or new formulations of existing drugs for **people suffering from neglected diseases**.
- To develop drugs for the **most neglected diseases** (such as sleeping sickness, leishmaniasis, and Chagas disease), while considering engagement in **R&D projects for other neglected patients** (e.g. malaria, paediatric HIV, filarial infections)
- To **strengthen capacities in a sustainable manner**, including through know-how and technology transfers in the field of drug R&D for neglected diseases.
- To adopt a **dynamic portfolio approach**

# Responding to the needs of patients suffering from neglected diseases



DNDi's PRIORITY:  
Neglected  
Patients



...from bench to bedside

+ incubation with  
WHO of:



# Address immediate patient needs & deliver innovative medicines: short- and long-term

*New chemical entities (NCEs)*

*New formulations*

*New indications for existing drugs*

*Completing registration dossier*

*Geographical extension*

Long-term projects

Medium-term projects

Short-term projects



Research



Translation



Development



Implementation

> 5  
years

3-5  
years

1-2  
years

# DNDi's success is only possible through innovative partnerships

Over 160 partnerships worldwide

## CRITERIA FOR SUCCESS

- ✓ Share the same vision
- ✓ Mutual understanding
- ✓ Involvement throughout the whole process

Biotechs

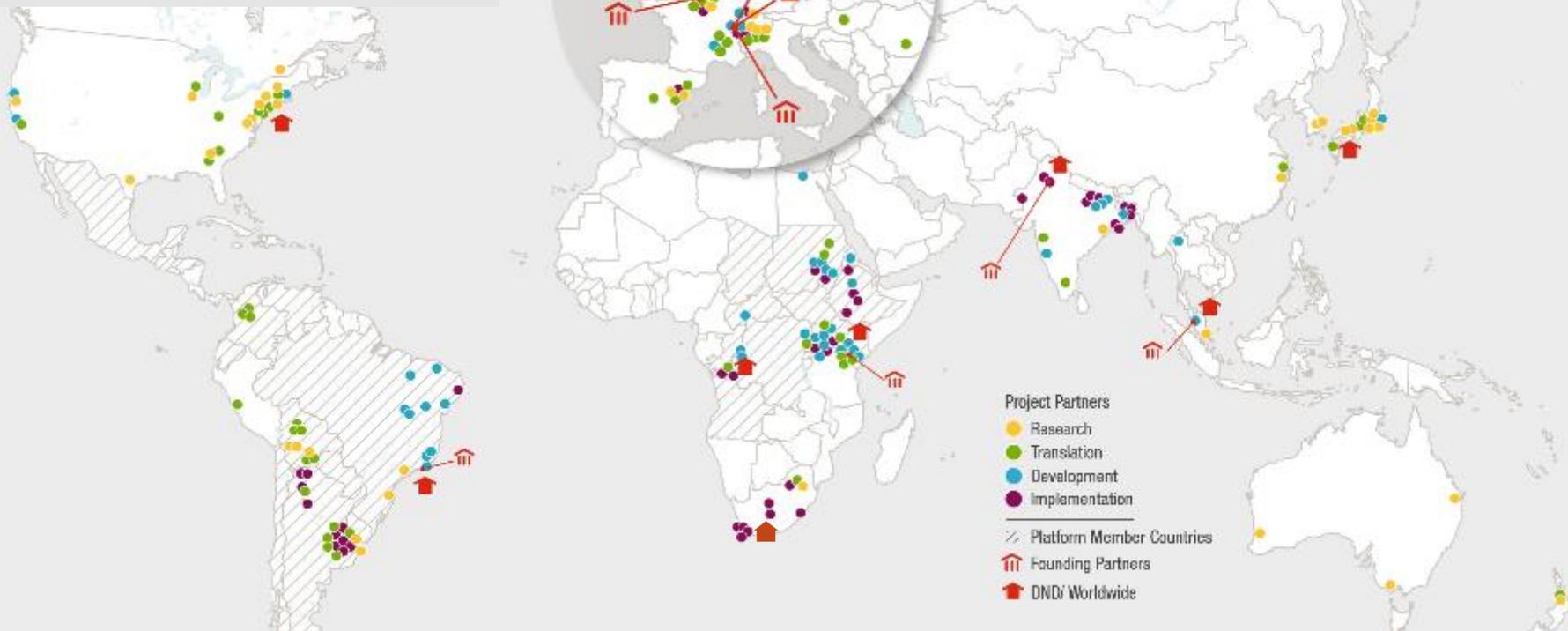
Int. Org. & NGOs

PDPs

Universities & Research Institutes

CROs

Pharmaceutical companies



# Partnering and research capacity building with MoHs and national control programmes

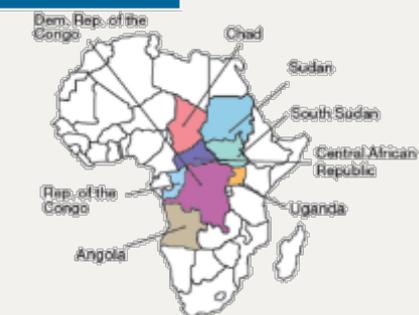
## VL



Major role of regional disease platforms:

- Strengthening local capacities
- Conducting clinical trials (Phase II/III studies)
- Facilitating registration
- Accelerating implementation of new treatments (Phase IV & pharmacovigilance studies)
- Defining patients' needs and target product profile (TPP)

## HAT



## CHAGAS



Countries highlighted on the map represent Chagas disease endemic Latin American countries with platform members. Many other CLCP members not shown on this map but are listed below.

# DNDi R&D Portfolio December 2018



	DISCOVERY			TRANSLATION			DEVELOPMENT		IMPLEMENTATION
	Screen	Hit to lead	Lead opt.	Pre-clinical	Ph I	Ph IIa/PoC	Ph IIb/III	Registration	Access
<b>HAT</b>			SCYX-1330682 SCYX-1608210				Acoziborole Fexinidazole T.b. rhodesiense		Nifurtimox-Eflornithine (NECT) Combination therapy Fexinidazole *
<b>LEISHMANIASIS</b>	✓	Leish H2L Booster H2L Daiichi-Sankyo LH2L	DNDI-5421 DNDI-5610 Amino pyrazoles CGH VL series 1 Leish L205 series	DNDI-5561 GSK3186899 DDD853651 GSK3494245 DDD1305143 CpG-D35 (CL)	DNDI-6148 DNDI-0690	New CL combination	New treatments for HIV/VL New treatments for PKDL MF/ Paromomycin combo for Africa	New VL treatments Latin America	SSG&PM Africa  New VL treatments Asia
<b>CHAGAS</b>	✓	Chagas H2L Booster H2L Daiichi-Sankyo CH2L	Chagas C205 series	Biomarkers		New Benz regimens +/- fosravuconazole Fexinidazole			Benznidazole Paediatric dosage form
<b>FILARIA</b>			Macro Filaricide 3	Oxfendazole	Emodepside ABBV-4083				
<b>MYCETOMA</b>							Fosravuconazole		
<b>PAEDIATRIC HIV</b>							'4-in-1' LPV/r/ABC/3TC	LPV/r pellets with dual NRTI	Superbooster Therapy Paediatric HIV/TB
<b>HCV</b>							Ravidasvir/ Sofosbuvir	Ravidasvir	
<b>MALARIA</b>									FDC ASAQ   FDC ASMQ

# 8 new treatments delivered since 2007



- ✓ Easy to use
- ✓ Affordable
- ✓ Field-adapted
- ✓ Non-patented



## 2007 **ASAQ** **Malaria**

>500 million patients reached



## 2011 **PAEDIATRIC BENZNIDAZOLE** **Chagas disease** **Two sources developed**



## 2008 **ASMQ** **Malaria**

Used in Africa and Asia



## 2011 **NEW VL TREATMENT ASIA** **Visceral leishmaniasis in Asia** **Support to disease elimination**



## 2009 **NECT** **Sleeping sickness**

100% of stage-2 patients



## 2016 **SUPERBOOSTER THERAPY** **Paediatric HIV** **Recommended by WHO**



## 2010 **SSG&PM** **Visceral leishmaniasis in E Africa** **Now 1st line in all countries**



## 2018 **FEXINIDAZOLE** **Sleeping sickness** **Approved by European Medicines Agency, first all-oral treatment**

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# Two phases of human disease



Haemolympathic (early) stage

In the classical model  
HAT is characterized by  
two phases

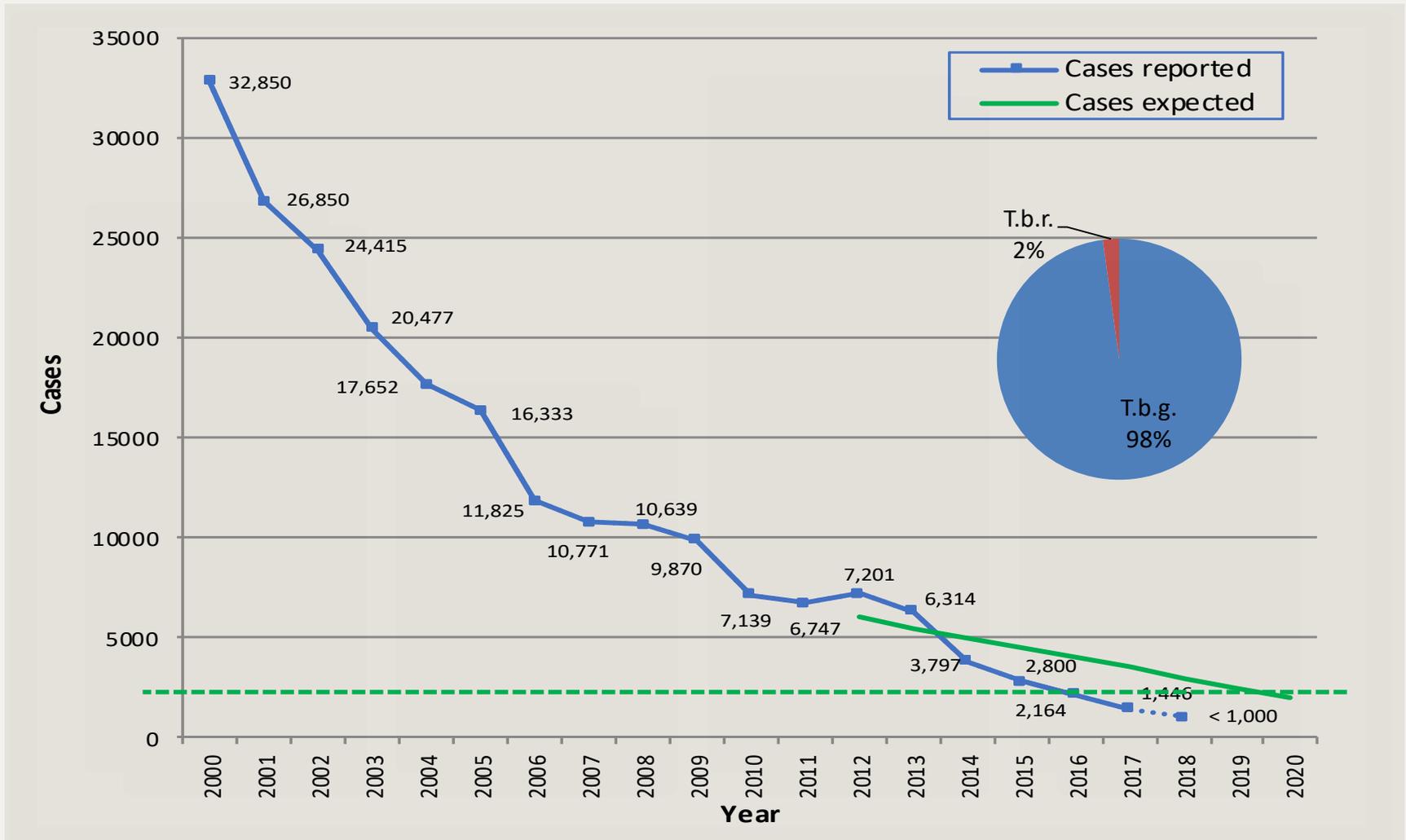
Clinical progression  
varies from  
patient to patient



Neurological (late) stage

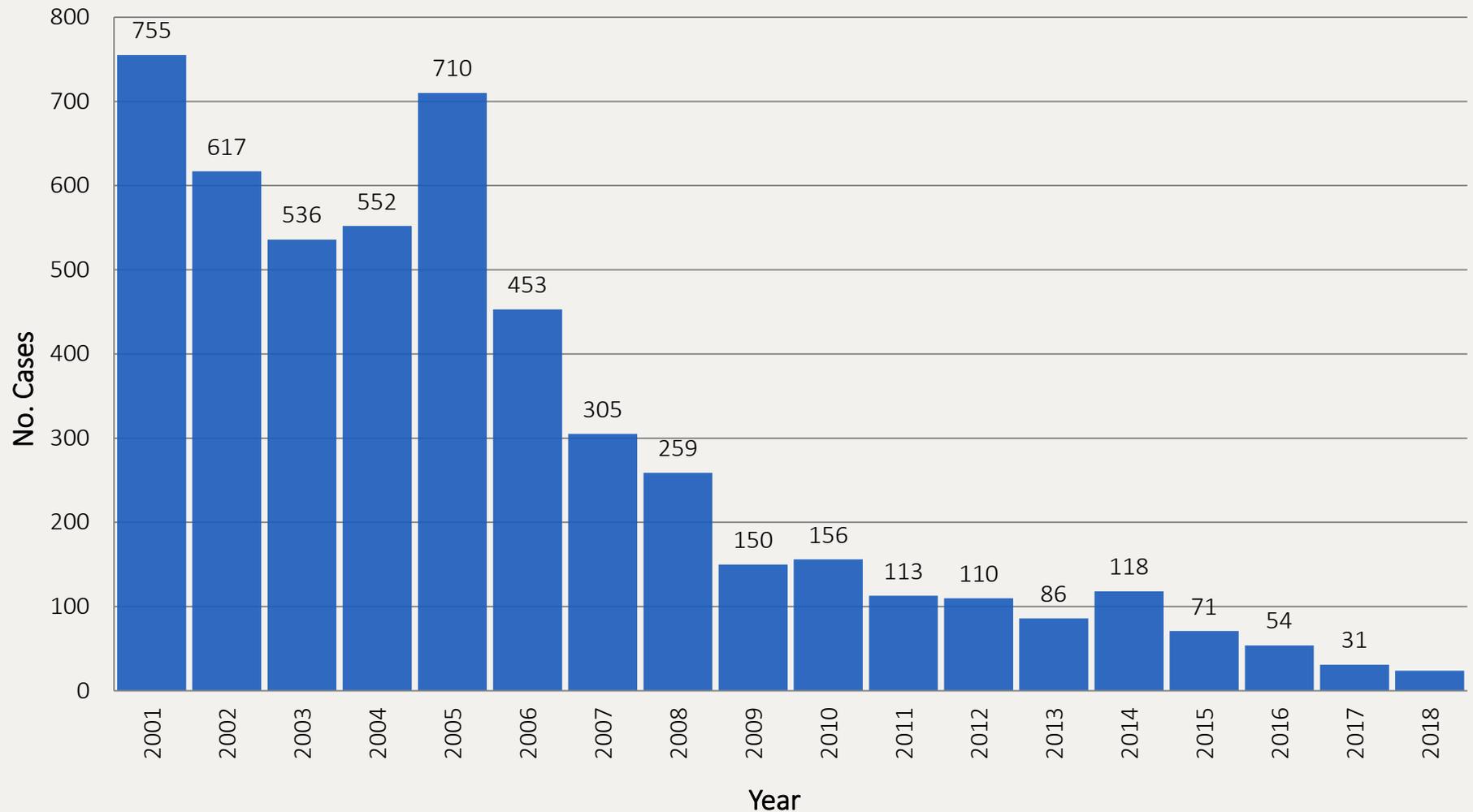
# HAT elimination: progress

- Number of new cases reported and WHO benchmark



# HAT elimination: progression

## Number of rHAT cases reported 2001-2018

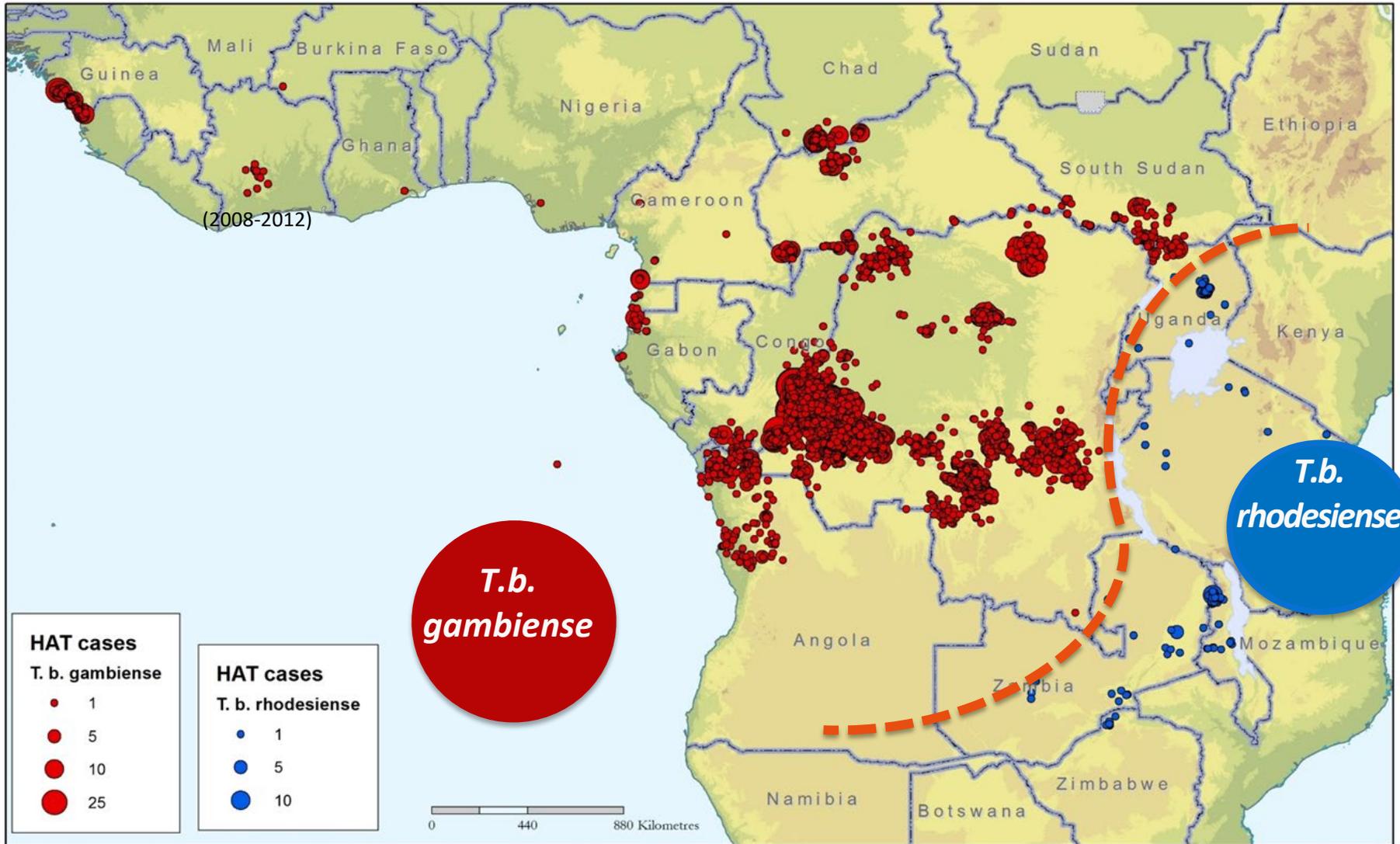


# The distribution of human African trypanosomiasis (2013-2017)

*The Atlas of human African trypanosomiasis*



Food and Agriculture  
Organization of the  
United Nations



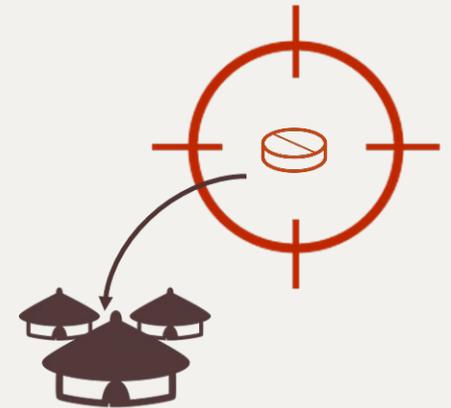
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO and FAO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

# Summary

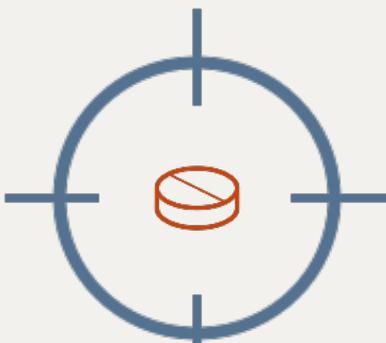
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# Target product profile:

- Effective in both stages
- Broad spectrum (*T.b. gambiense* and *rhodesiense*)
- Clinical efficacy >90% at 18 month follow up
- Safe for pregnant and breastfeeding women
- Adult and paediatric formulation
- No need to monitor for adverse effects
- Maximum 10 days orally once a day
- Stability in zone 4 during >3 years
- Cidal
- <30€/ treatment\* (cost of drug)



# Sleeping sickness: two new treatments in development to support sustainable elimination



15 years ago

Melarsoprol:

Toxic, resistant



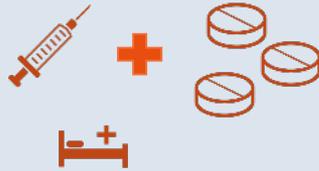
Eflornithine:

Not available

Since 2009

NECT

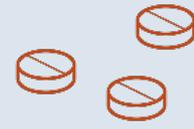
Improved therapy



2018

Fexinidazole

Oral treatment  
(10 days)



Future objective

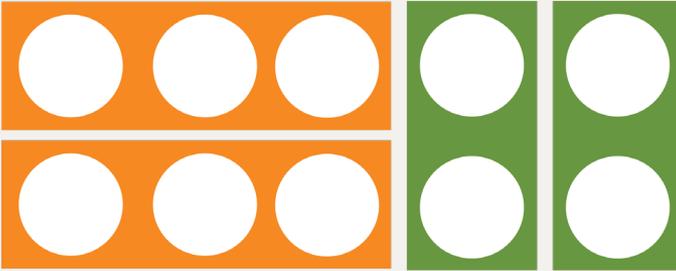
Acoziborole

Single-dose,  
oral treatment



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# HAT-r-ACC

- To extend the indication of fexinidazole for the treatment of r-HAT (WP1)
- To ensure proper execution of clinical trials through strengthening capacity of treatment and care (WP2)
- To engage the local community to improve treatment access and extend case detection (WP3)



# Partners in HAT-r-ACC

## *DNDi Project coordination and trial management*

- **Direct intervention**
- Makerere (Uganda)  
*Trial lead and Social Sciences*
- UNHRO (Uganda)  
and MoH (Malawi)  
*Trial execution and Community intervention*
- **Training and follow up**
- IHMT Lisboa Medical
- Swiss TPH Good Clinical Practice
- IRD France Laboratory
- Epicentre France Data management

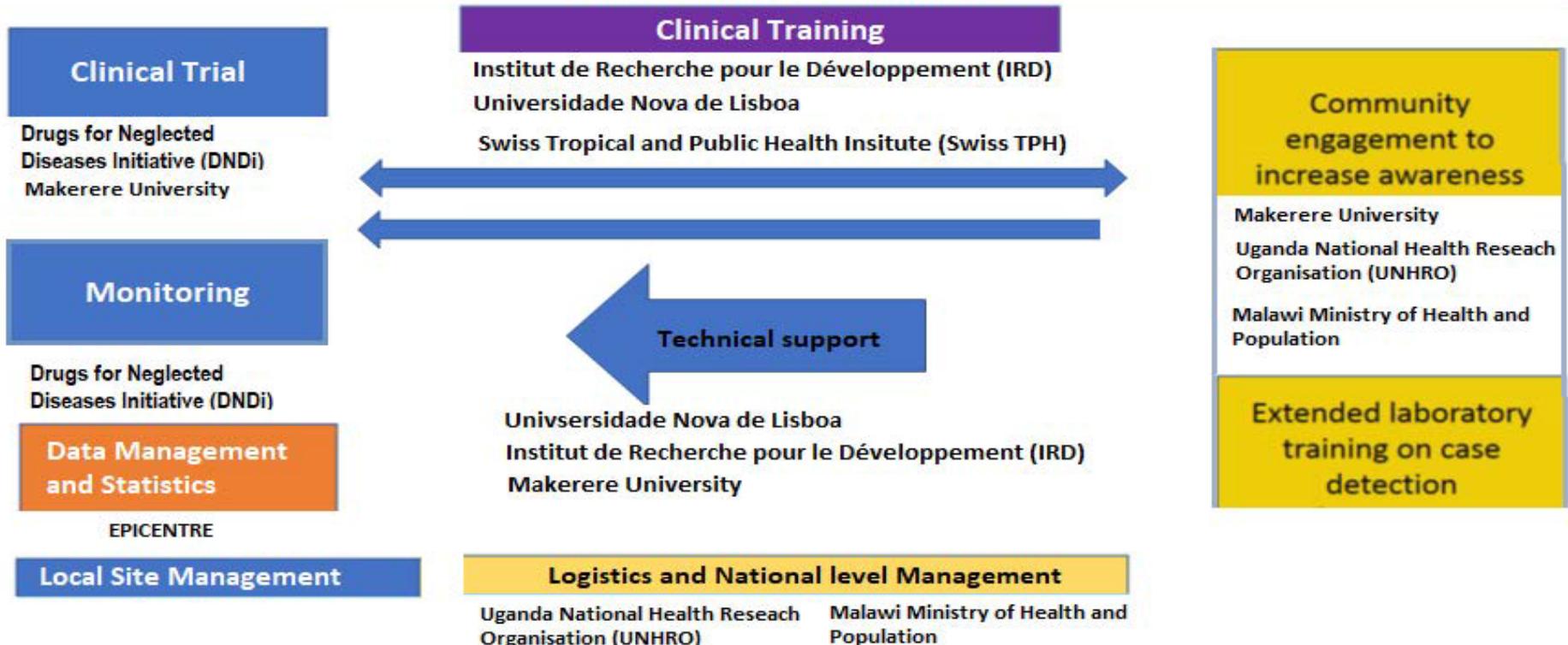
**WP4 : Drugs for Neglected Diseases Initiative (DNDi)**

**Project Management Committee (PMC)**

Drugs for Neglected Diseases Initiative (DNDi), Institut de Recherche pour le Développement (IRD), Universidade Nova de Lisboa, Makerere University, Malawi Ministry of Health and Population, Uganda National Health Research Organisation (UNHRO), Swiss Tropical and Public Health Institute (Swiss TPH), EPICENTRE

**Project Advisory Committee (PAC), EDCTP acting as observer**

**Consortium Management (HAT-r-ACC)**



**WP1 : Drugs for Neglected Disease Initiative (DNDi)**  
(Lead)

**WP2 : Institut de Recherche pour le Développement (IRD) & Universidade Nova de Lisboa**  
(Lead)

**WP3 : Makerere University**  
(Lead)

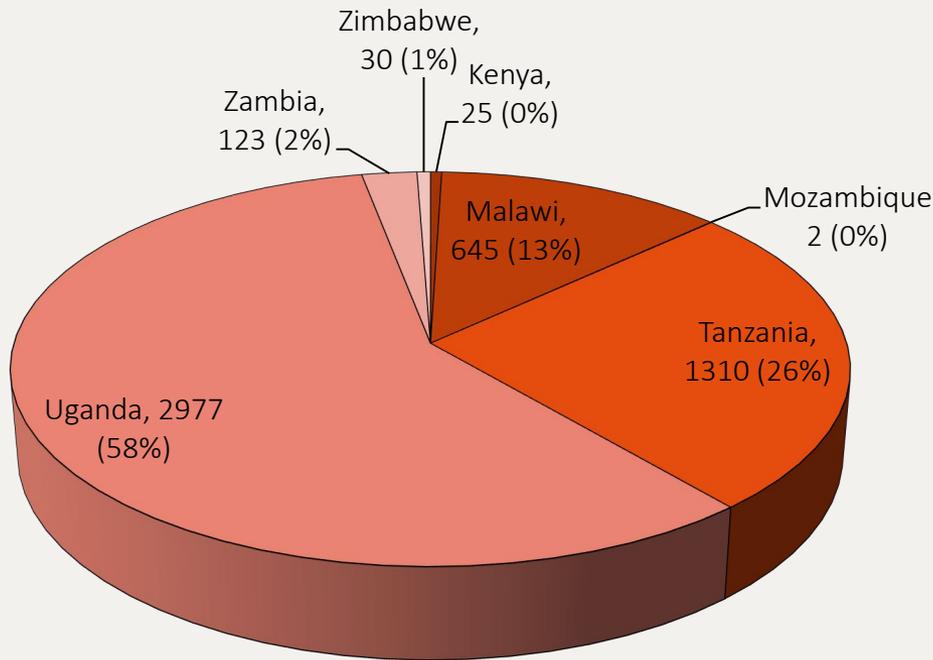
Communication, dissemination and exploitation of results supported by activities including HAT-r-ACC consortium and HAT platform interactions with key stakeholders and target audiences ensuring high level of information exchange

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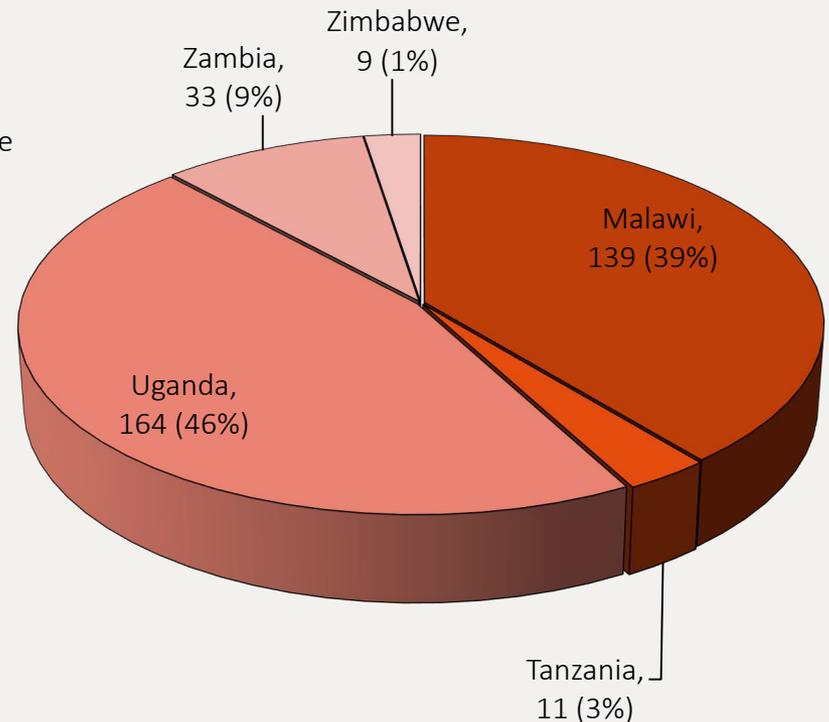
# Cases by country *T. b. rhodesiense*

2001-2017

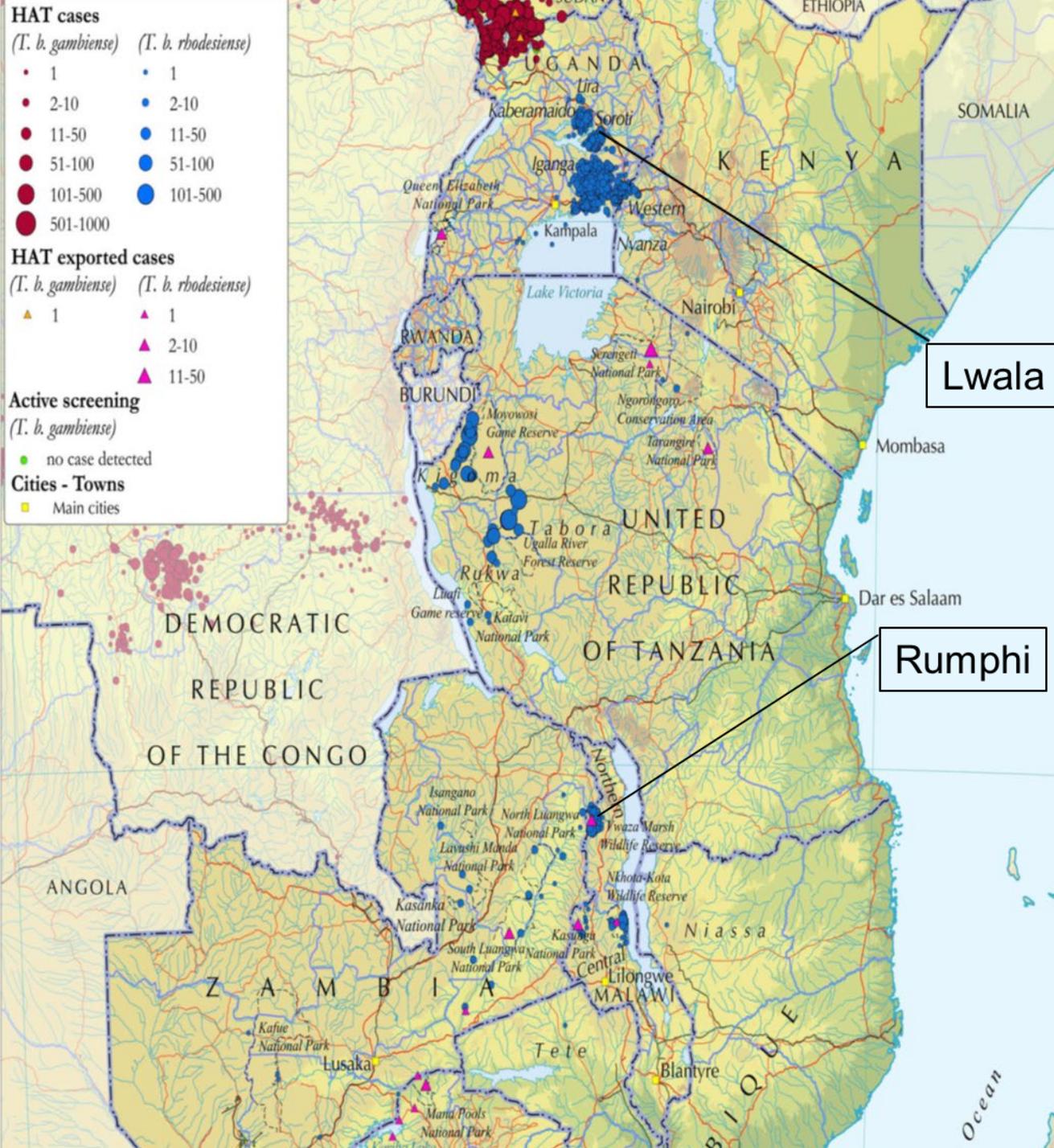


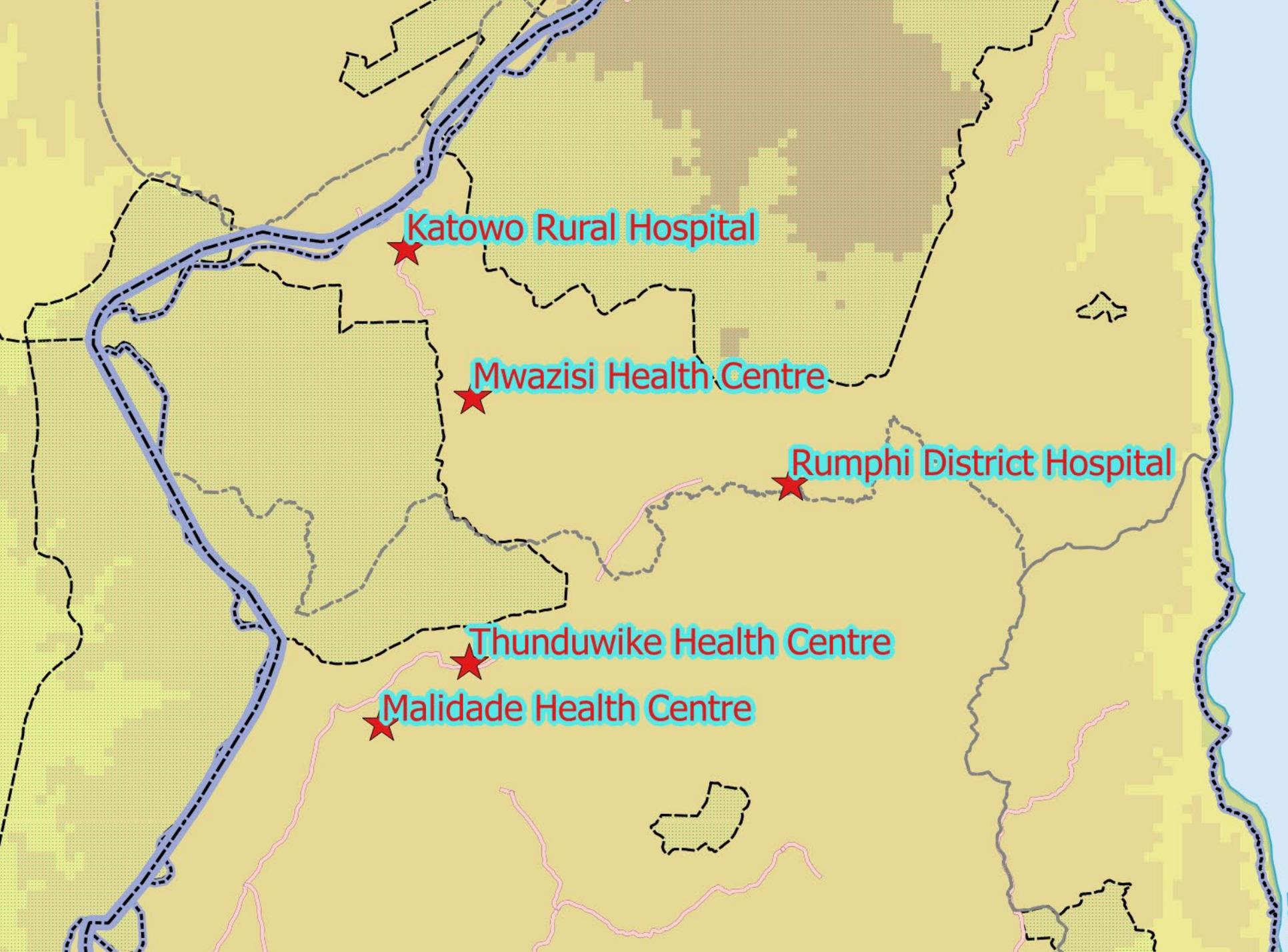
5,134 cases declared

2013-2017



356 cases declared





Katowo Rural Hospital

Mwazisi Health Centre

Rumphidze District Hospital

Thunduwike Health Centre

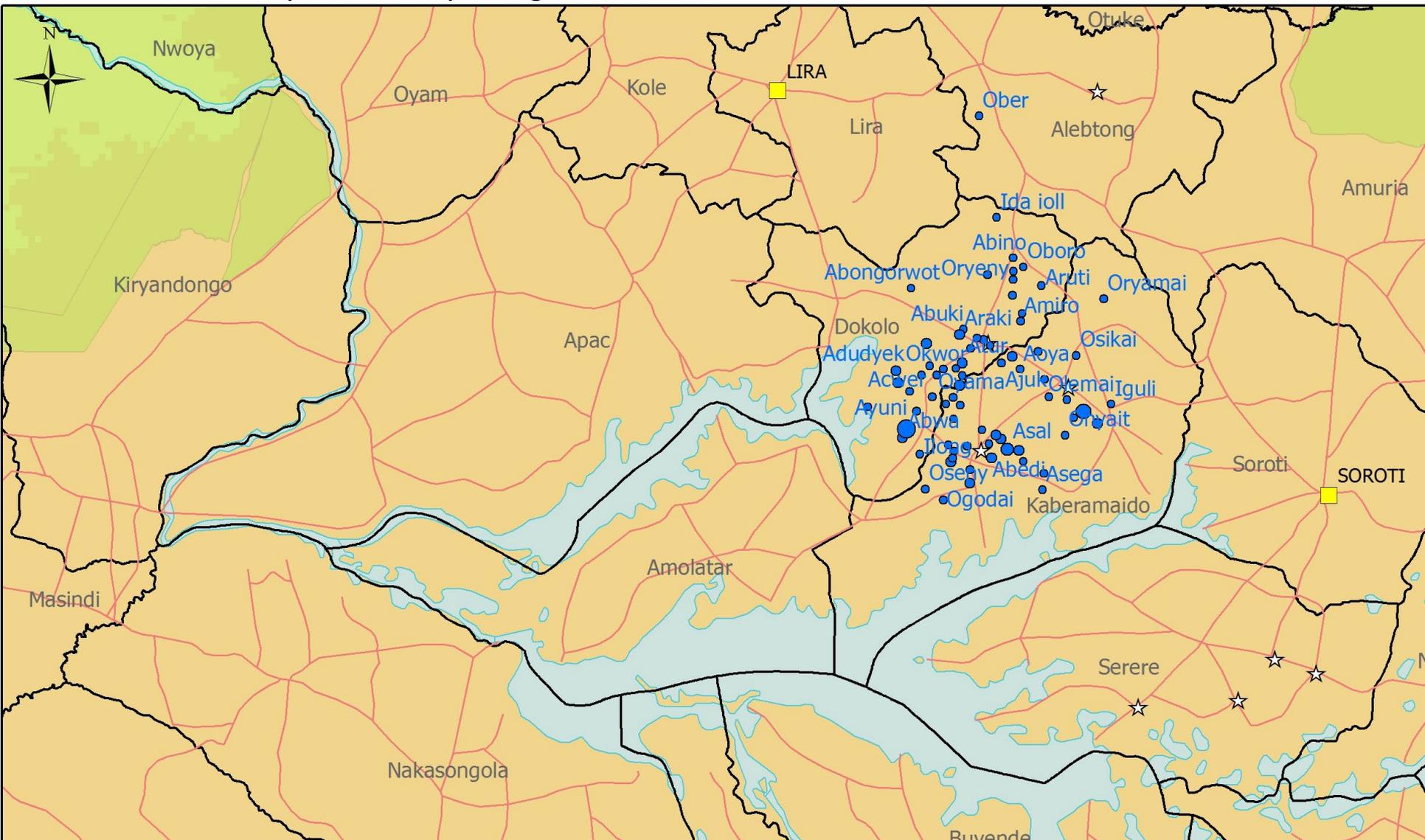
Malidade Health Centre



# Number of HAT cases (2014-2016) in South-Eastern Uganda

Atlas of human African trypanosomiasis (2000-2016)

Version: June 2018. Optimised for printing in A3 format



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# Clinical Trial

- Protocol Number: DNDi-FEX-07-HAT
- Study title: Efficacy and safety of fexinidazole in patients with human African trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: A multicentre, open-label clinical trial
- Design: multicentre, open-label, non-randomized
- Recruitment target: 34 evaluable stage-2 r-HAT patients
- Study sites :
  - Lwala Hospital (Uganda)
  - Rumphi District Hospital (Malawi)
  - Patients from neighbouring Health centers: Kaberamaido/Dokolo Districts (Uganda) and Rumphi/Mzimba North District (Malawi) and Chama (Zambia) will be transported to the sites for treatment

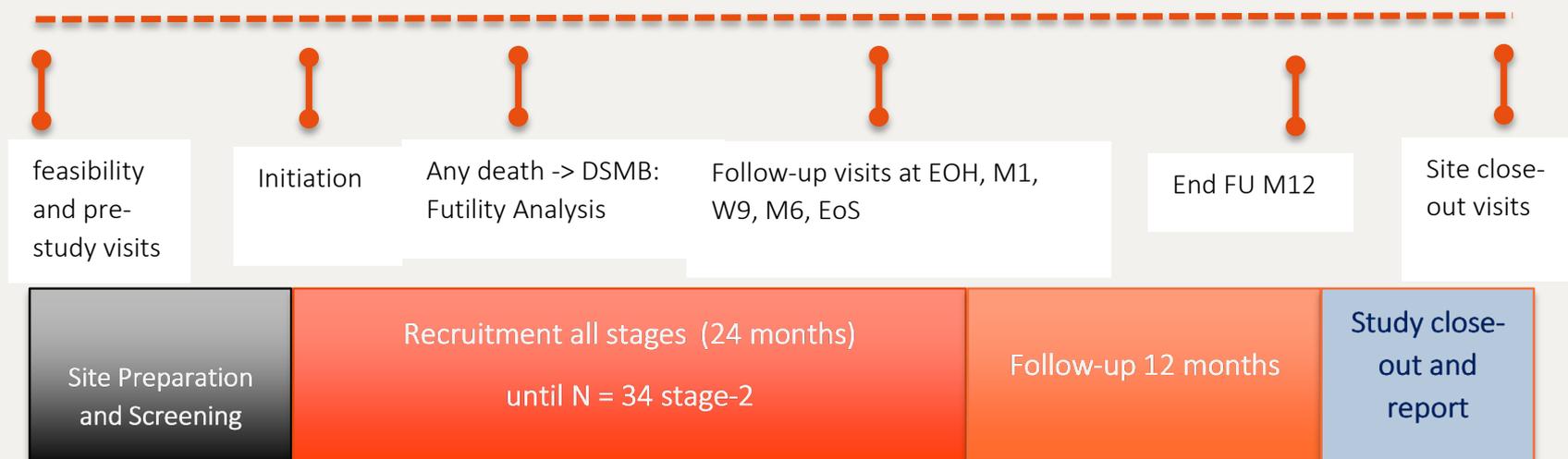
# Trial Objectives and Endpoints

## Ultimate Objective:

→ To show that fexinidazole offers an alternative over melarsoprol in stage-2 r-HAT patients and over suramin in stage-1 r-HAT patients

# Study duration

- 2 years recruitment and 1-year follow-up
- If the recruitment of 34 evaluable stage-2 patients is shorter than 2 years, the duration of the study can be shortened.
- Each patient's participation will be 12 to 13 months



# Investigators

- Principal Investigator:
  - Prof. Dr. Enock Matovu
  - Makerere University
- Coordinating Investigators:
  - Uganda: Charles Wamboga: Ministry of Health
  - Malawi: Marshal Lemerani, Ministry of Health
- Site Investigators:
  - Lwala (Uganda): Dr Eriatu Anthony
  - Rumphu (Malawi): Dr Westain Nyirenda

# DNDi thanks all the HAT donors



Thank you

