Implementation of a Simplified Diagnostic Algorithm in an Endemic Area of Colombia

Colin Forsyth, PhD, MPH

Chagas Treatment Access Project

Drugs for Neglected Diseases *initiative*

DNDi's Access Approach for Chagas Disease

- If we develop an ideal treatment tomorrow, will it reach patients in need? Will it reach them on time?
- **Vision**: Apply the same bold innovation and partnership approach that has fuelled DNDi's success in clinical research to overcoming the multifactorial barriers which hamper access to diagnosis and treatment for people with Chagas disease around the world
- **Elements**
  - **Partnership model**
  - **Pilot approach**
  - **Build success cases**

DNDi's Chagas Access Implementation Project: **Selected Pilot Countries/Regions**

Country	pop. *T. cruzi* +	Rank
Brazil	1,157,000	2
Mexico	876,000	3
Colombia	438,000	5
USA	347,000	6
Guatemala	167,000	10

Challenges in Screening and Diagnosis of Chagas Disease

- >90% of patients undiagnosed
- Symptoms/lack of symptoms
- No gold standard
- Variability of test performance
  - Across tests: Various products based on different principles
  - Across populations
    - *T. cruzi* genetic diversity
    - Geographic differences in immune response
    - Cross reaction with leish or *T. rangeli*
  - Across individuals in the same population
  - Overestimation of test characteristics
  - Lack of systematic quality control
- Regulatory barriers
- Health system
  - Lack of routine screening in primary care
  - Need for multiple tests
  - Low awareness

Colombia’s Chagas Treatment Access Pilot Project

Colombian Pilot Project: Participants

MinSalud
Ministerio de Salud y Protección Social

Gobierno DEPARTAMENTAL

Unidad Administrativa Especial de Salud Arauca

Instituto Nacional de Salud

Gobernación de Boyacá

SESALUB
Secretaría de Salud de Boyacá

Secretaría de Salud

DNDi
Drugs for Neglected Diseases *initiative*

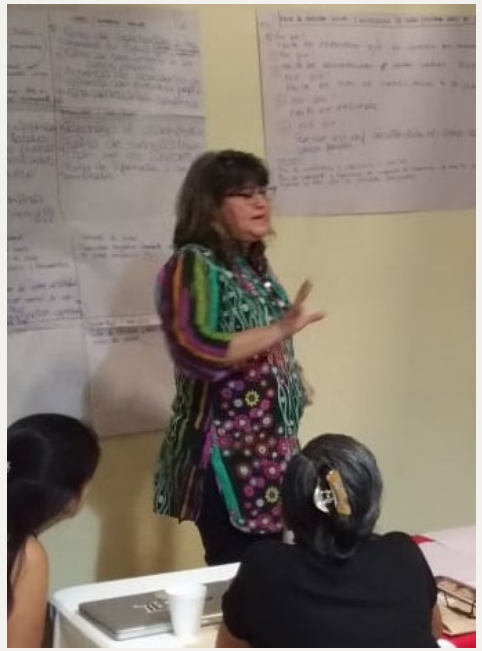
Gobernación de Casanare

Secretaría de Salud de Casanare

PROGRAMAS DEPARTAMENTALES DE ETV

Andres Caicedo
National Parasitological Reference Laboratory, National Institute of Health, Colombia

Carolina Florez, National Parasitological Reference Laboratory, National Institute of Health, Colombia

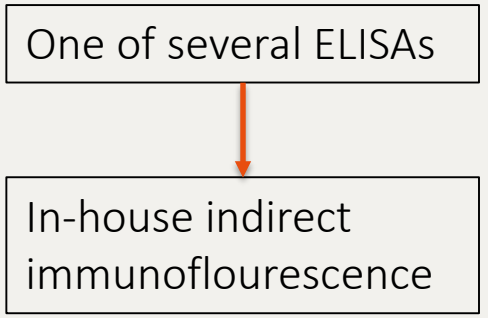


Andrea Marchiol, DNDI

Rafael Herazo, DNDI

Colombia's Diagnostic Process Before the Pilot Project

- Epidemiological context[1]
  - Estimated prevalence: 438,000 people
  - At-risk population: 4.8 million
  - Predominance of *T. cruzi* I, but other scenarios also common
- Barriers seminar (2015)
- The Problem
  - Only 1.2% of at-risk population screened
  - Significant barriers to obtaining confirmatory testing[2]
- Bottlenecks
  - Reliance on various tests for screening in departmental laboratories; their performance in Colombian samples largely unknown
  - Low availability of testing in primary care
  - Use of in-house indirect immunofluorescence for confirmation



1. World Health Organization. Chagas disease in Latin America: An epidemiological update based on 2010 estimates. Weekly Epidemiological Record 2015;6:7.
2. Cucunubá ZM, Manne-Goehler JM, Díaz D, et al. How universal is coverage and access to diagnosis and treatment for Chagas disease in Colombia? A health systems analysis. Social Science & Medicine 2017;175:187-98.

Difficulties using the IFA as a confirmatory test

- Difficult to find commercially available reagents
- Reagents produced in-house, hard to scale up production
- Highly operator-dependent, requires extensive training to use equipment
- High costs for equipment, including ongoing maintenance
- Requires dark room dedicated to its use
- Not automated
- Not included in insurance plans, patients had to self-pay
- Difficult to decentralize; only available in reference centers

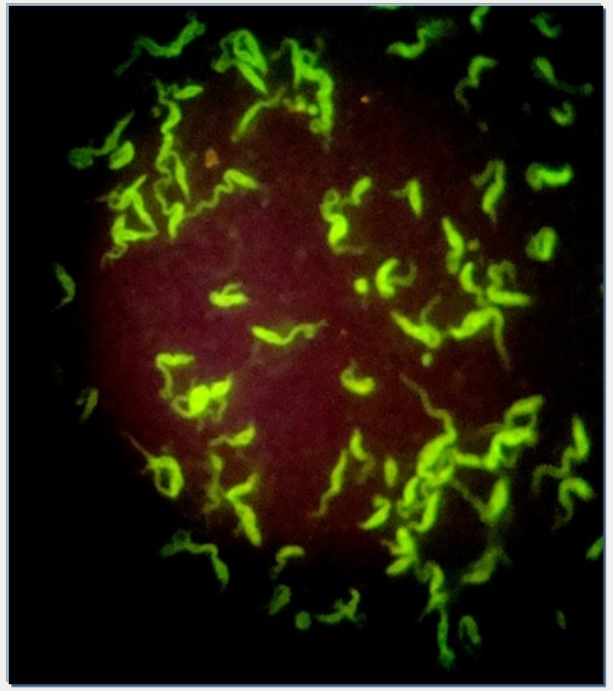
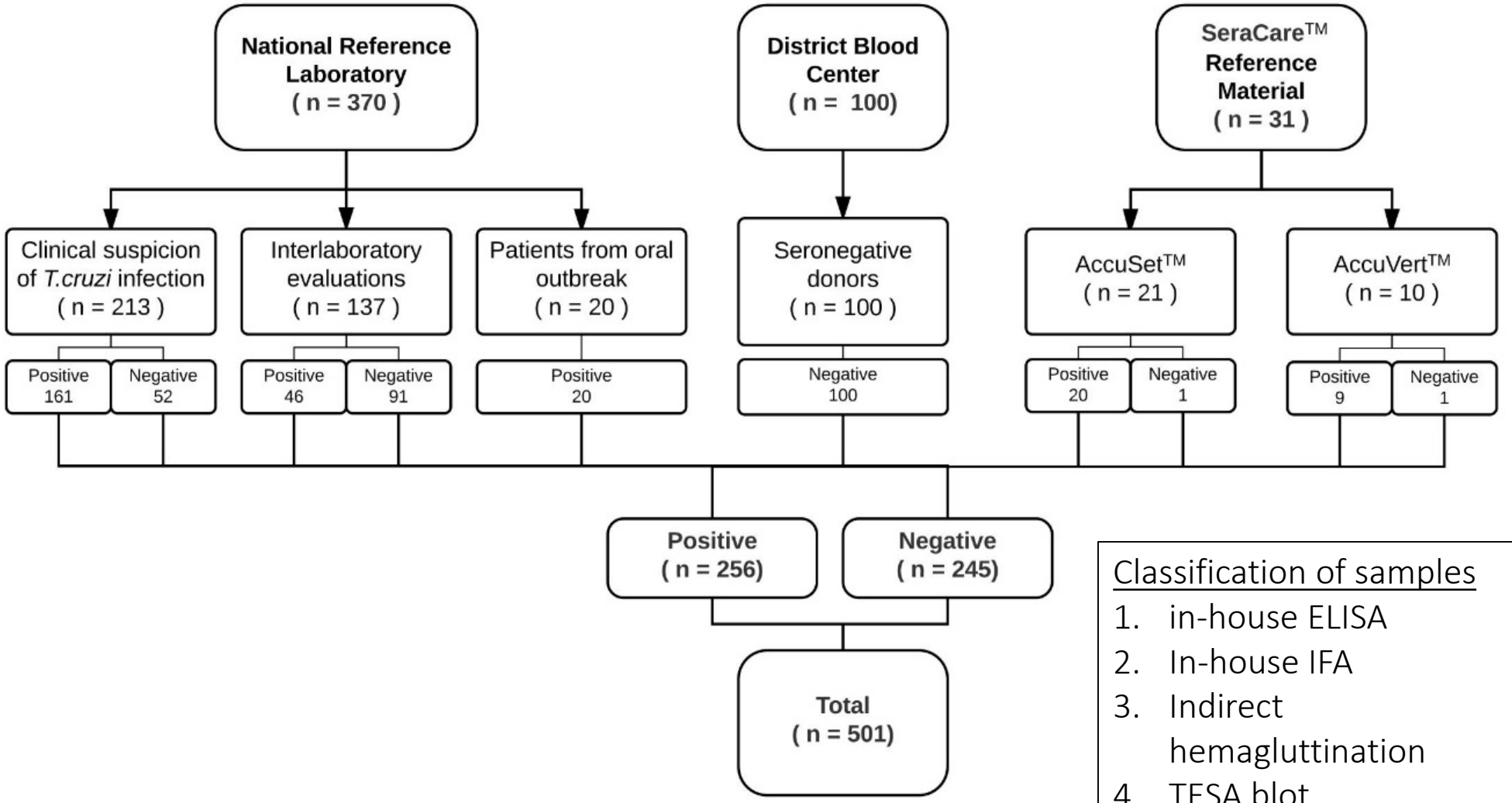


Photo courtesy of National Institute of Health, Colombia

Assessment of Colombia's Diagnostic Algorithm

- Research question: Could a new diagnostic algorithm based on commercially available assays perform as well as the standard algorithm?
- 2016: National Reference Laboratory (LNR) and National Health Institute (INS) undertook a validation study with support from DNDi's Chagas Access Consultative Group (Maria Isabel Jercic)
- Study design: (lead investigators Andres Caicedo and Carolina Flores, LNR)
  - Manufacturers of tests commercially available in Colombia invited to participate in validation study
  - Colombian blood samples from diverse sources assembled (n=501)
  - WHO reference panel utilized
  - Sensitivities, specificities calculated.
  - Performance characteristics estimated for both sequential and parallel use of paired tests of different types

Sample Composition: Colombian Validation Study



Classification of samples

1. in-house ELISA
2. In-house IFA
3. Indirect hemagluttination
4. TESA blot

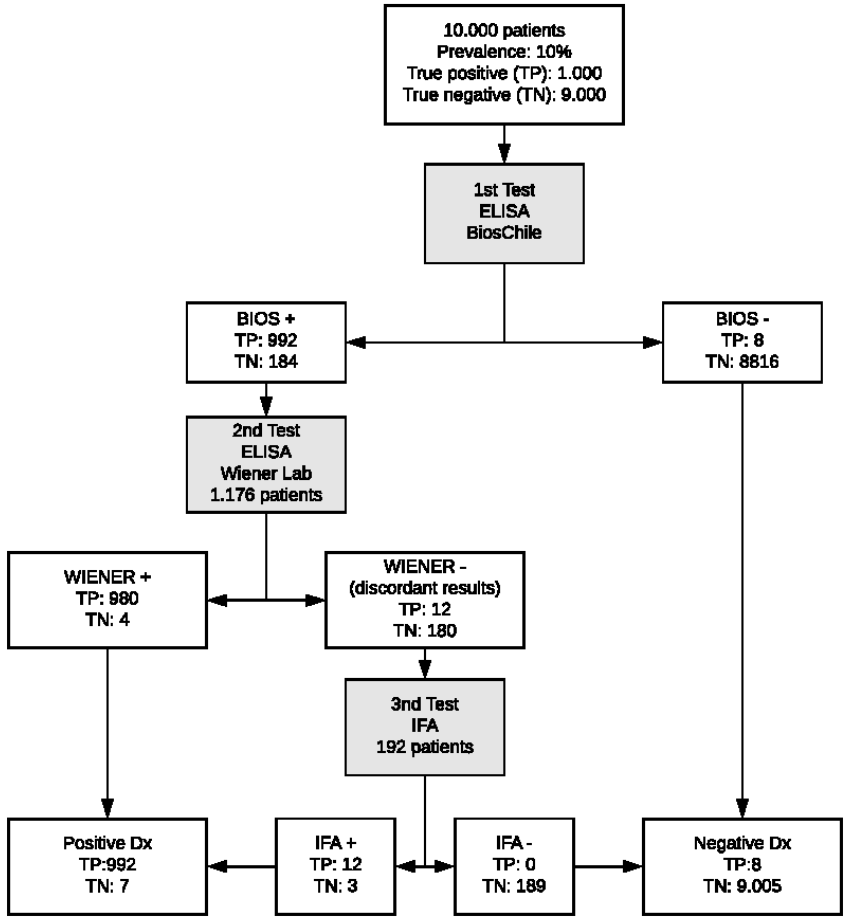
Commercial *T. cruzi* immunoassays evaluated, Colombia

Immunoassay	Manufacturer	Abbreviation[1]	Antigens	Reader used	Sensitivity (%)[2]	Specificity (%)[2]
Conventional method (total antigen)						
Test ELISA Chagas III	Grupo BIOS (Santiago, Chile)	BIOS	Total antigen + membrane antigens	spectrophotometer	100	100
Nonconventional methods						
Synthetic peptides						
Umelisa Chagas	Tecnosuma International (Havana, Cuba)	SUMA	Peptide 17 &18	Fluorometer (SUMA Technology)	100	100
Recombinant antigens						
Architect System Chagas	Abbott (Germany)	ARCHI	FP3, FP6, FP10 & TcF	Abbot i1000SR immunoassay analyzer	99-100	99-100
BioELISA Chagas	Biokit (Barcelona, Spain)	BIOKIT	TcD, TcE, PEP2, TCL1, TCL2	spectrophotometer	100	97·4-99·5
Chagatest ELISA rec v4	Wiener Lab. (Rosario, Argentina)	WIENER	SAPA, Ag1, Ag2, Ag13, Ag30 & Ag 36	spectrophotometer	99·13-100	98·30-99·66
T. cruzi AB	Diagnostics Bioprobes (Milan, Italy)	DIAPRO	No data	Gemini XPS microplate reader	100	>99·5
Chagas ELISA IgM + IgG	Vircell Microbiologists (Granada, Spain)	VIRCEL	FRA, B13, MACH (PEP2, TcD, TcE, SAPA)	spectrophotometer	100	98

Operational characteristics of immunoassays evaluated for detection of *T. cruzi* in Colombian patients

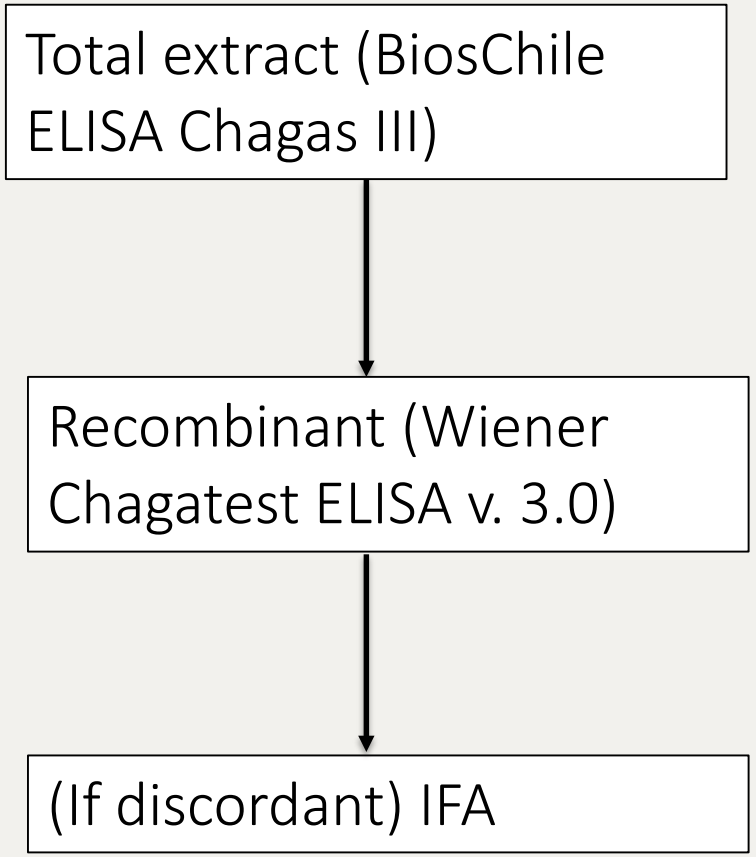
Immunoassay	False negatives	False positives	Sensitivity % (CI95%)	Specificity % (CI95%)	PPV % (CI95%)
BIOS	2	5	99·22 (97·94-100)	97·96 (95·98-99·93)	98·07 (96·20-99·94)
VIRCEL	1	6	99·61 (98·65-100)	97·55 (95·41-99·69)	97·7 (95·69-99·71)
WIENER	3	5	98·83 (97·31-100)	97·96 (95·98-99·93)	98·06 (96·19-99·94)
ARCHI	4	5	98·44 (96·72-100)	97·96 (95·98-99·93)	98·05 (96·17-99·94)
BIOKIT	5	13	98·05 (96·16-99·94)	94·69 (91·68-97·70)	95·08 (92·28-97·88)
DIAPRO	11	7	95·70 (93·02-98·38)	97·14 (94·85-99·43)	97·22 (94·99-99·45)
SUMA	19	6	92·58 (89·17-95·98)	97·55 (95·41-99·69)	97·53 (95·37-99·69)

Predicted outcomes: 2-stage testing, BIOS+WIENER



Development of a New Diagnostic Algorithm

- Based on study results, new algorithm developed using two ELISAs based on different antigenic principles
- Implementation
  1. Formalized by INS, March 2017
  2. New algorithm utilized in vector certification process, 23 municipalities in 2017



ADVANTAGES OF THE NEW ALGORITHM

Previous Algorithm	New Algorithm
Not covered by insurance.	Covered by insurance.
2-3 blood draws in different facilities; patients travel to departmental capitals for second and third tests.	Only one blood draw in a facility closer to patients, eliminating need for costly travel.
In-house production of reagents.	Commercially available reagents.
Extensive training of personnel; complex, expensive equipment.	Use of automated readers available in most private and public laboratories
Different equipment for each test.	Use of same equipment for both tests.
Subjective interpretation of results.	Automated results.
Unclear guidelines for screening tests.	Evidence-based guideline for screening, complementary tests.

Impact of the New Diagnostic Algorithm: Department of Casanare, Colombia

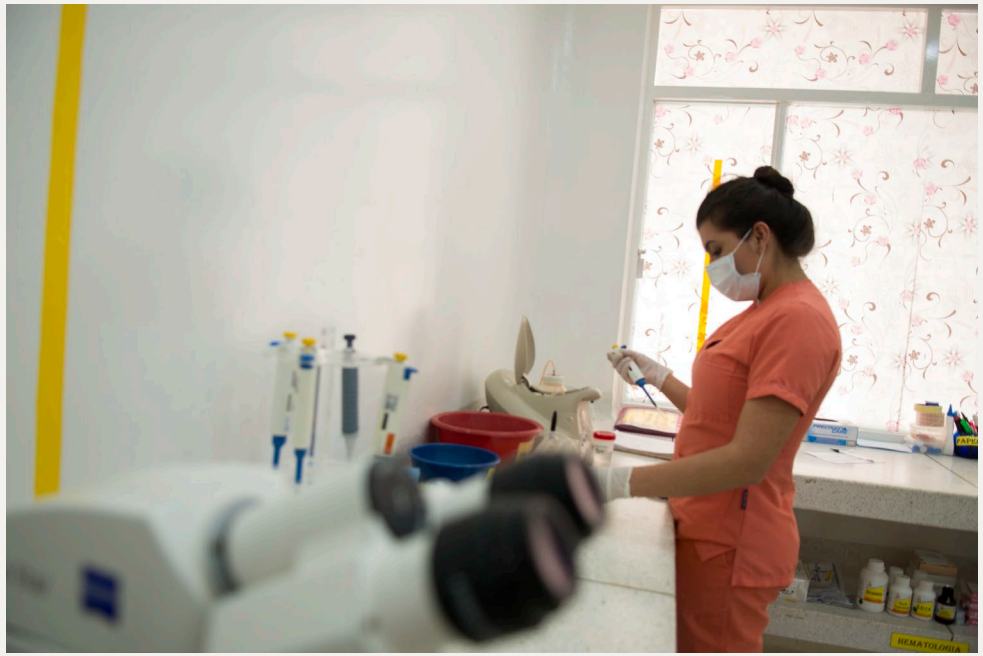
Indicator		12 months prior (2016)	Y1 of Pilot (March 2017-March 2018)	Net change	% change
Mean days between medical order and availability of confirmed results	Total	364	17	-347	-95
	Nunchía	306	13	-293	-96
	Tamara	510	21	-489	-96
People screened	Total	35	384	+349	+997
	Nunchía	25	197	+172	+688
	Tamara	10	187	+177	+1770
People confirmed +	Total	12	95	+83	+692
	Nunchía	10	59	+49	+490
	Tamara	2	36	+34	+1700

Comparison of Days to Confirmation in Casanare: New Colombian Diagnostic Algorithm

Category		N (%)	Mean days	P
Gender	Men	127 (33.1)	14.07	0.001
	Women	257 (66.9)	18.42	
Community	Támara	187 (48.7)	21.14	<0.001
	Nunchia	197 (51.3)	13.04	
Insurance	Contributive	47 (12.2)	14.85	0.276
	Subsidized	316 (82.3)	17.50	
	ND	21 (5.5)		
Serology	-	288 (75.0)	14.44	0.058
	+	95 (24.7)	17.86	
Age group	<20	90 (23.4)	17.44	0.158
	20-39	135 (35.2)	19.00	
	40-59	109 (28.4)	15.54	
	60+	50 (13.0)	17.02	
Total		384 (100.0)	16.98	

Breakdown of mean delays elapsed, Colombian *T. cruzi* diagnostic process

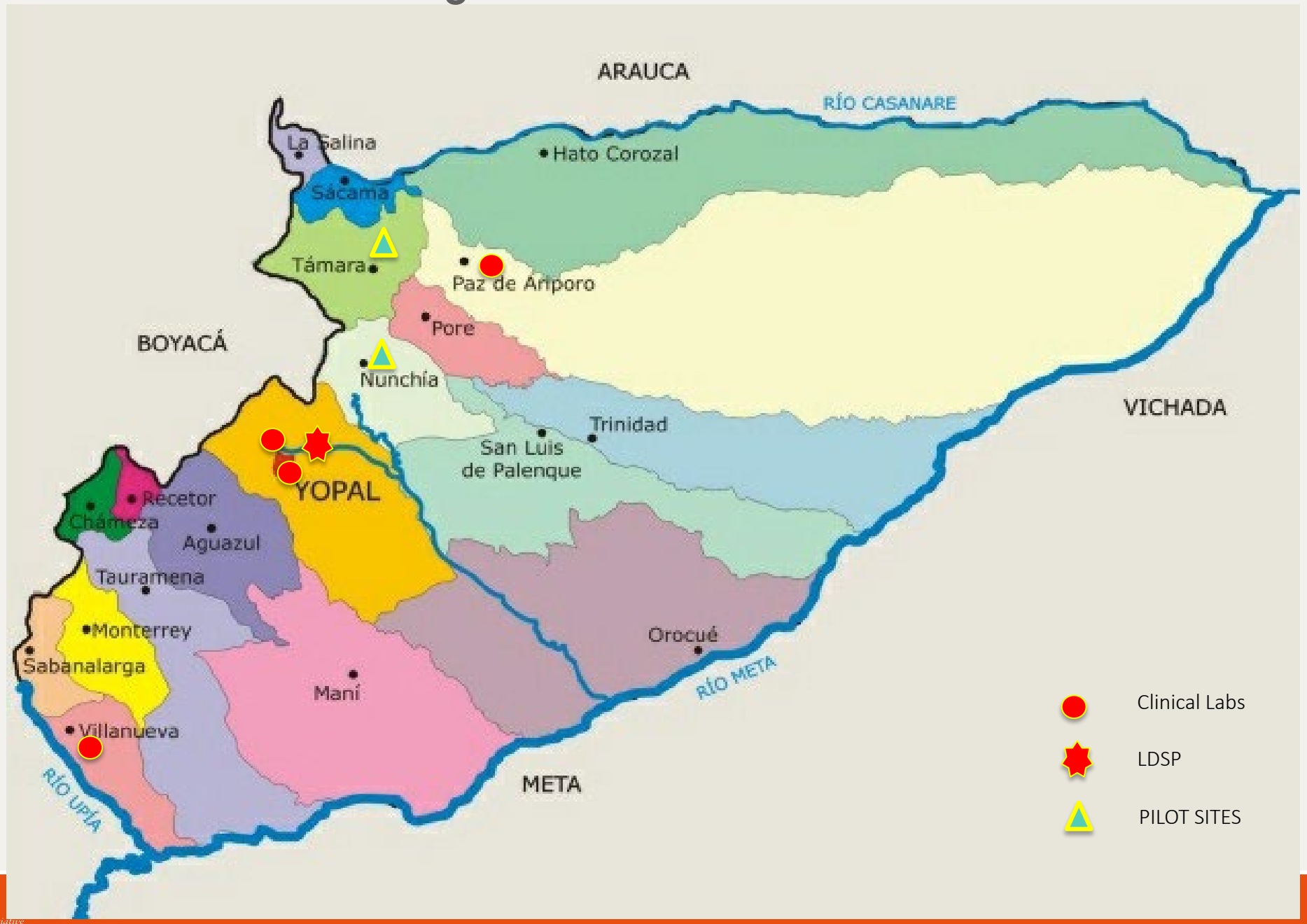
	Medical order-blood draw	Blood draw-sent to lab	Received lab-resultad sent	**Total process**
Tamara	6.55	5.20	8.98	21.14
Nunchia	0.44	3.67	7.91	13.04
Total	3.41	4.41	8.43	16.98



Serological Results: Pilot Project, Casanare

Category		*T. cruzi*+	*T. cruzi* -	Prevalence (%)	OR (CI)	p
Gender	Men	66	191	25.7	1.16 (0.70-1.91)	0.570
	Women	29	97	23.0		
Community	Támara	59	138	29.9	1.78 (1.11-2.86)	0.016
	Nunchia	36	150	19.4		
Insurance	Contributive	84	232	26.6	1.34 (0.64-2.81)	0.439
	Subsidized	10	37	21.3		
Age group	**<20**	4	85	4.5	0.11 (0.04-0.30)	<0.001
	20-39	23	112	17.0	0.50 (0.30-0.85)	0.009
	40-59	39	70	35.8	2.17 (1.3-3.53)	0.002
	60+	29	21	58.0	5.59 (3.00-10.42)	<0.001
Total		95	289	24.7		

Growth of the Diagnostic Network in Casanare



Next steps: Colombian Treatment Access Project

- Currently being introduced in five new communities
- National Reference Laboratory assisting with training in new pilot project (Guatemala)
- Remaining challenges for access to trypanocides (not registered in Colombia)
- Long-term role of DNDi?

Thank you!

The Drugs for Neglected Diseases *initiative* is grateful to its donors, public and private, who have provided funding to DND*i* since its inception in 2003. A full list of DND*i*'s donors can be found at http://www.dndi.org/donors/donors/.