PRIORITY NEEDS FOR DENGUE RESEARCH:
A WHO/TDR PERSPECTIVE

Comprehensive Review of the 'State of the Art' meeting for the prevention and control of dengue in the Americas

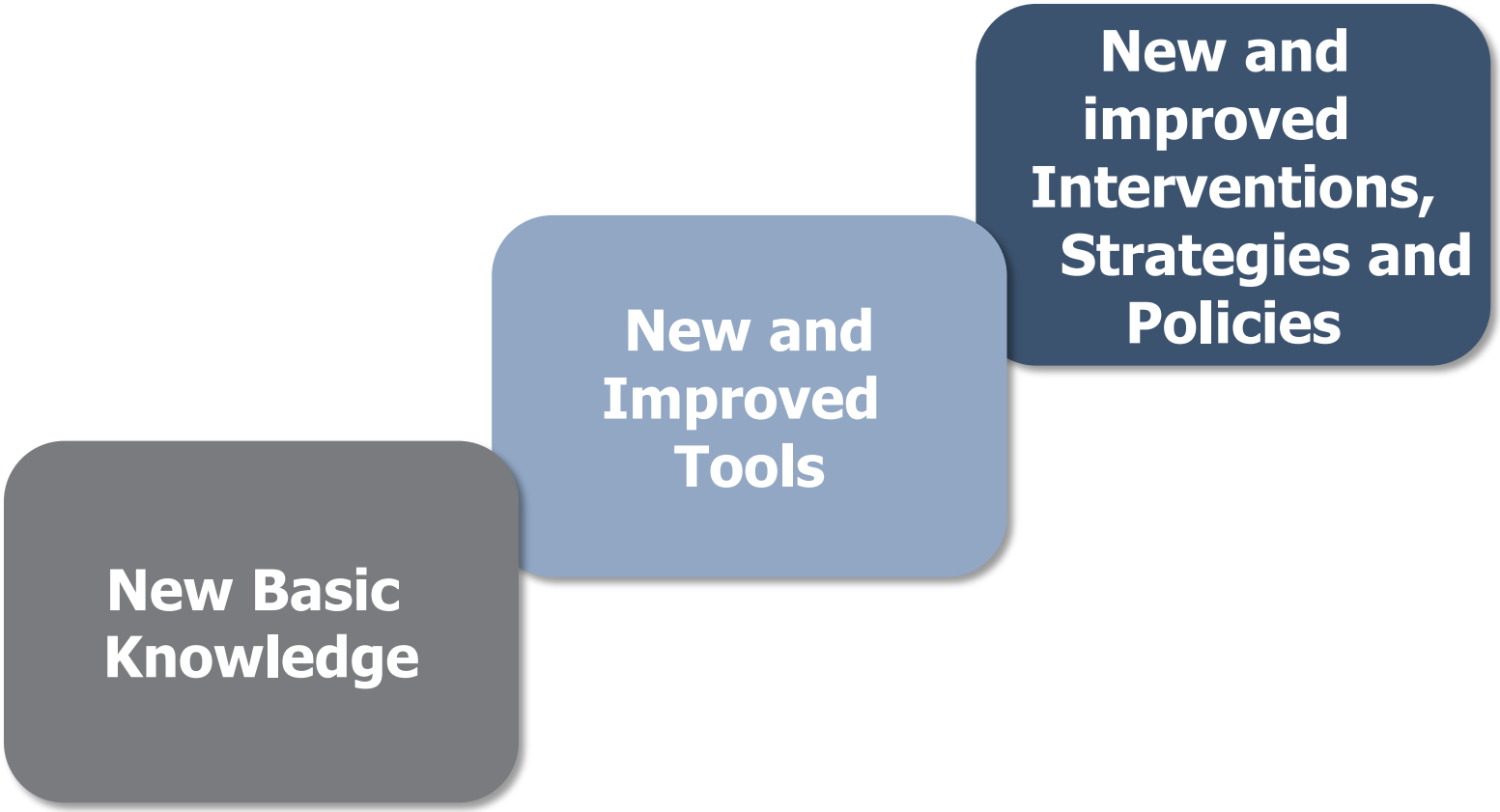
PAHO, Washington DC 28-29th May 2014

P. Olliaro, J. Sommerfeld, B. Arana, M. Guillerm, Y. Toure, A. Kroeger

World Health Organization

40 YEARS TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

RESEARCH NEEDS AT DIFFERENT LEVELS



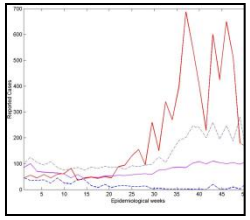
TDR DENGUE RESEARCH STREAMS

Improved case classification & management High quality diagnostics

New vector control tools & strategies

Improved knowledge of delivering dengue services through comprehensive approaches

Improved evidence of dengue outbreak detection & response



Case management

Vector control

Outbreak response

COST-EFFECTIVE IMPLEMENTATION STRATEGY

REDUCED CASE FATALITY & INCIDENCE

CLINICAL DENGUE CASE CLASSIFICATION & MANAGEMENT

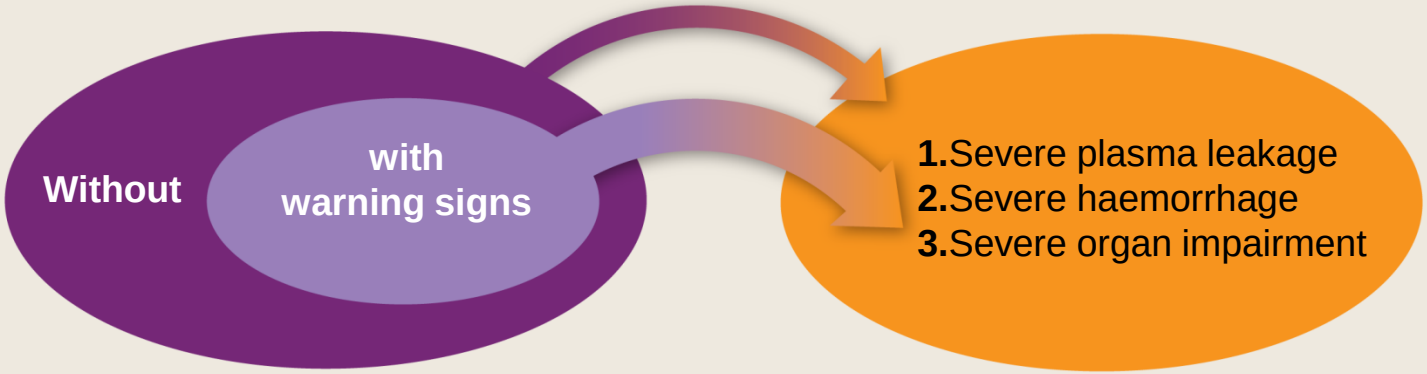
CLINICAL DENGUE

- Completed: **Revised classification** based on 1) systematic literature reviews; 2) prospective DENCO study; 3) 18-countries study showing clinicians preference for the revised classification
- On-going: Validity of **warning signs** tested in 1) predictive value study of warning signs in 8 countries (being analysed); 2) extensive IDAMS study on warning signs on ~10,000 patients (expected 2016)
- **ICD codes:** new ICD web version allows to report in the old or new classification system. Hard-copy version of ICD expected 2016.

Dengue case classification by severity

Dengue ± warning signs

Severe dengue



Criteria for dengue ± warning signs

Probable dengue
Live in/travel to dengue endemic area. Fever and 2 of the following criteria:
- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leucopenia
- Any warning sign

Laboratory confirmed dengue
(important when no sign of plasma leakage)

Warning signs*
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy; restlessness
- Liver enlargement >2cm
- *Laboratory:* Increase in HCT concurrent with rapid decrease in platelet count

** Requiring strict observation and medical intervention*

Criteria for severe dengue

1. Severe plasma leakage
leading to:
- Shock (DSS)
- Fluid accumulation with respiratory distress

2. Severe bleeding
as evaluated by clinician

3. Severe organ involvement
- Liver: AST or ALT>=1000
- CNS: Impaired consciousness
- Heart and other organs

STEPS FOR REVISING THE DENGUE CASE CLASSIFICATION

Reporte & publications describing the difficulties using DF/DHF/DSS

A systematic review of the issue
Bandyopadhyay S et al., TMIH 2006, 11 pp 1238–1255

DenCo study (dengue&control)
Alexander N et al, TMIH, 16 pp 936–948 , 2011

DF/DHF/DSS application study
Santamaria R et al, International Health (2009) 1, 133—140

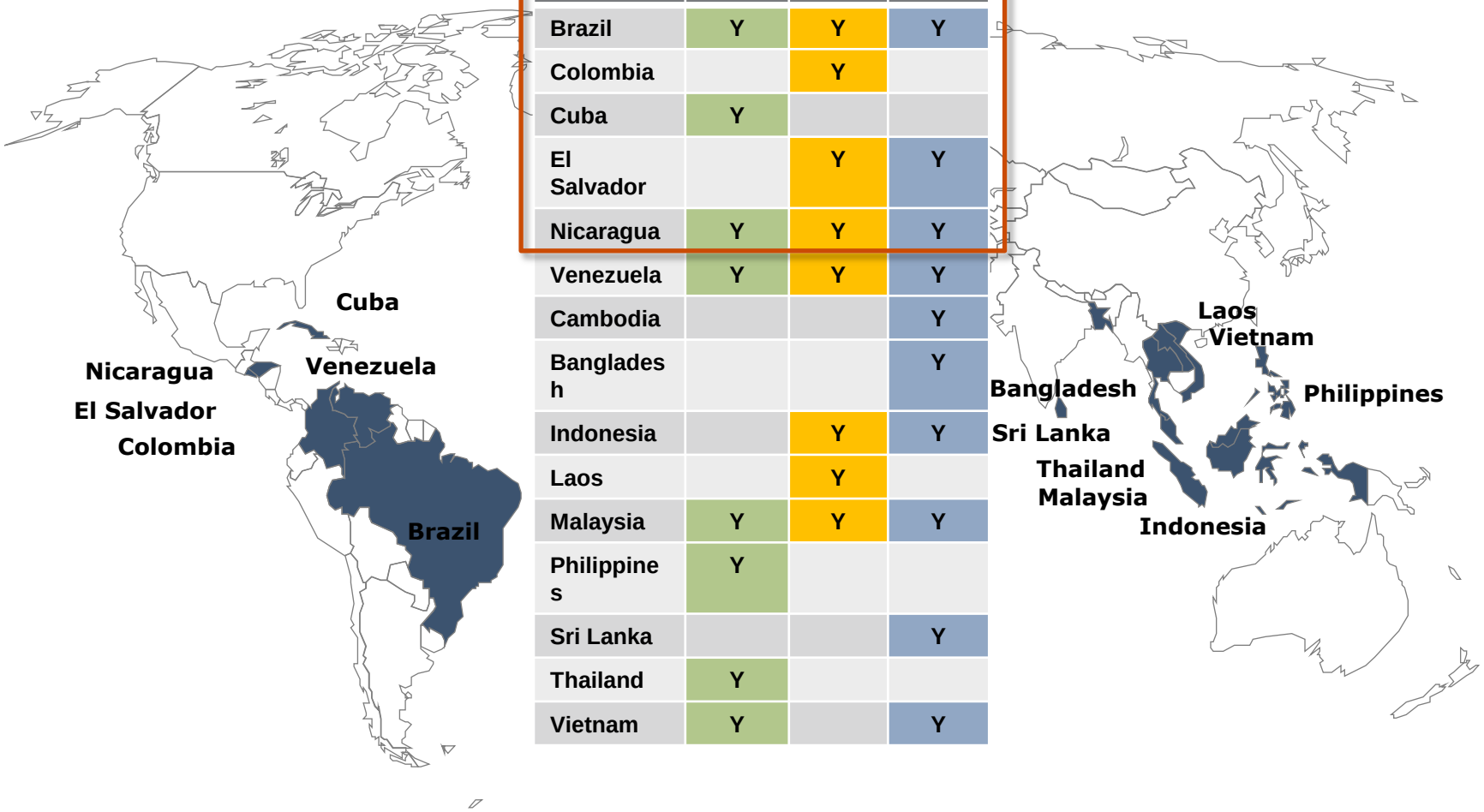
Four expert consensus meetings
La Habana and Kuala Lumpur 2007/09

Global expert consensus meeting
WHO Geneva 2008

Dengue guidelines validation study
Barniol J et al, *BMC Infectious Diseases* 2011, 11:106

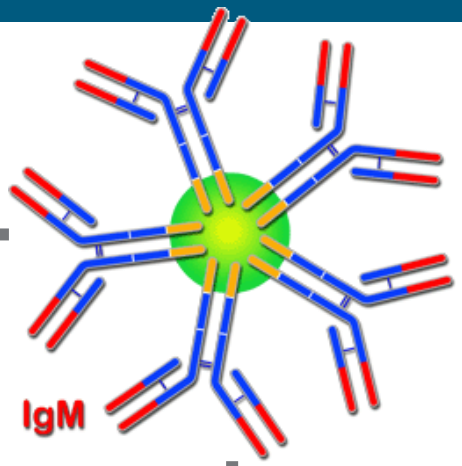
Systematic review of Revised dengue case classification
Horstick O et al, accepted Am J Trop Med Hyg

WARNING SIGNS STUDIES



Country	DENCO	TDR	IDAMS
Brazil	Y	Y	Y
Colombia		Y	
Cuba	Y		
El Salvador		Y	Y
Nicaragua	Y	Y	Y
Venezuela	Y	Y	Y
Cambodia			Y
Bangladesh			Y
Indonesia		Y	Y
Laos		Y	
Malaysia	Y	Y	Y
Philippines	Y		
Sri Lanka			Y
Thailand	Y		
Vietnam	Y		Y

DENGUE DIAGNOSTICS PERFORMANCE EVALUATION

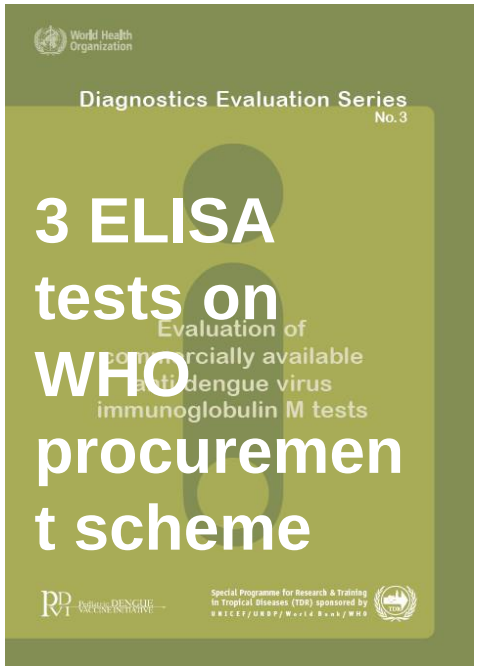


ROUND 1
RDT, ELISA

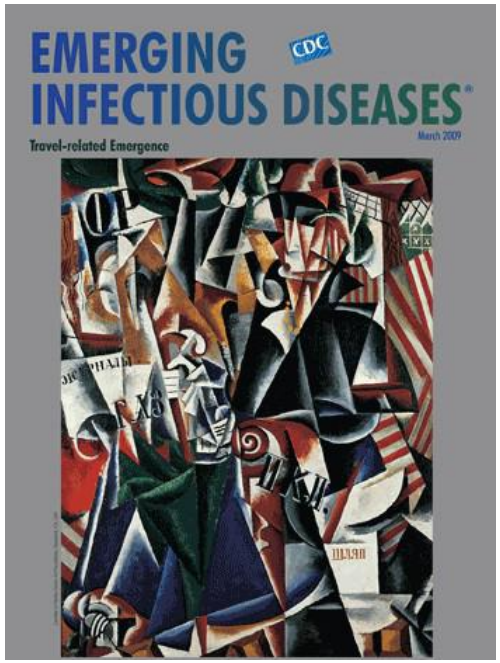
IgM

NS1

Glycoprotein 46-50 kDa.
Membrane (mNS1) & secreted (sNS1).
Elicits Abs with CF activity.
Antigen group, complex, type
T cell epitopes.

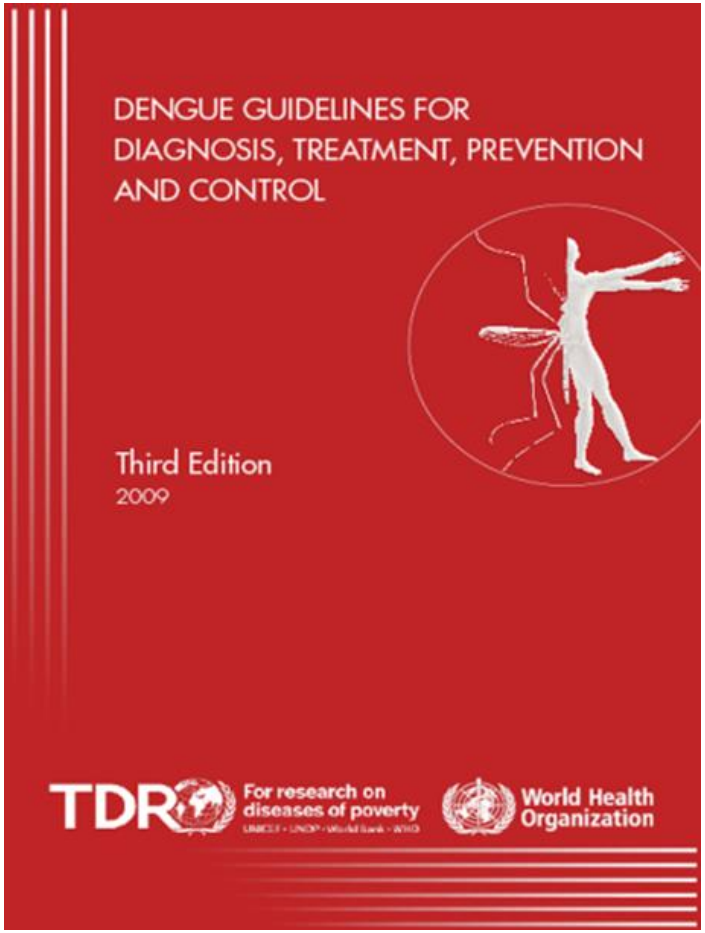


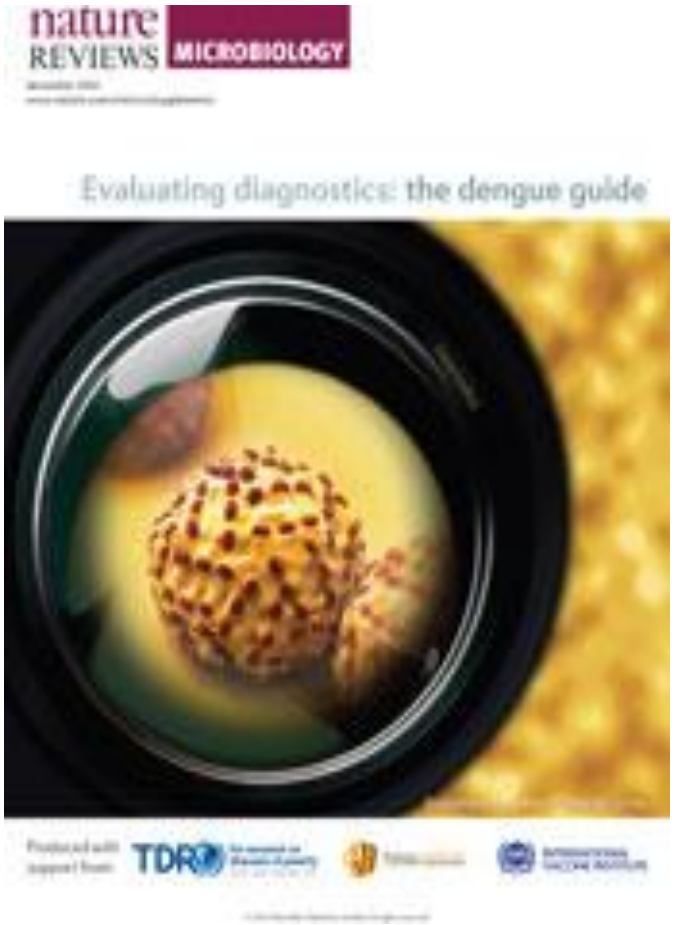
3 ELISA tests on WHO procurement scheme



ROUND 2
RDT, ELISA

OTHER PUBLICATIONS

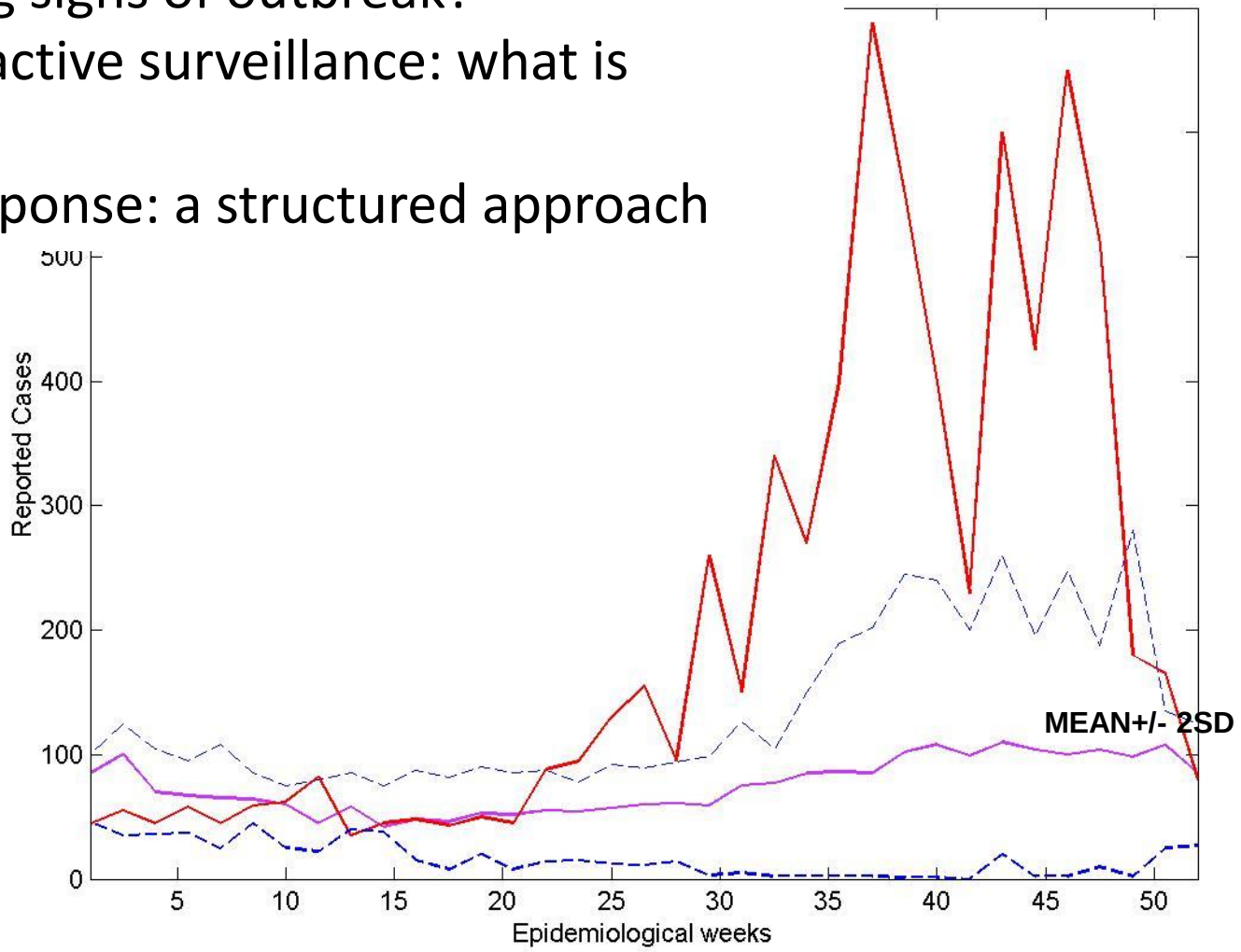




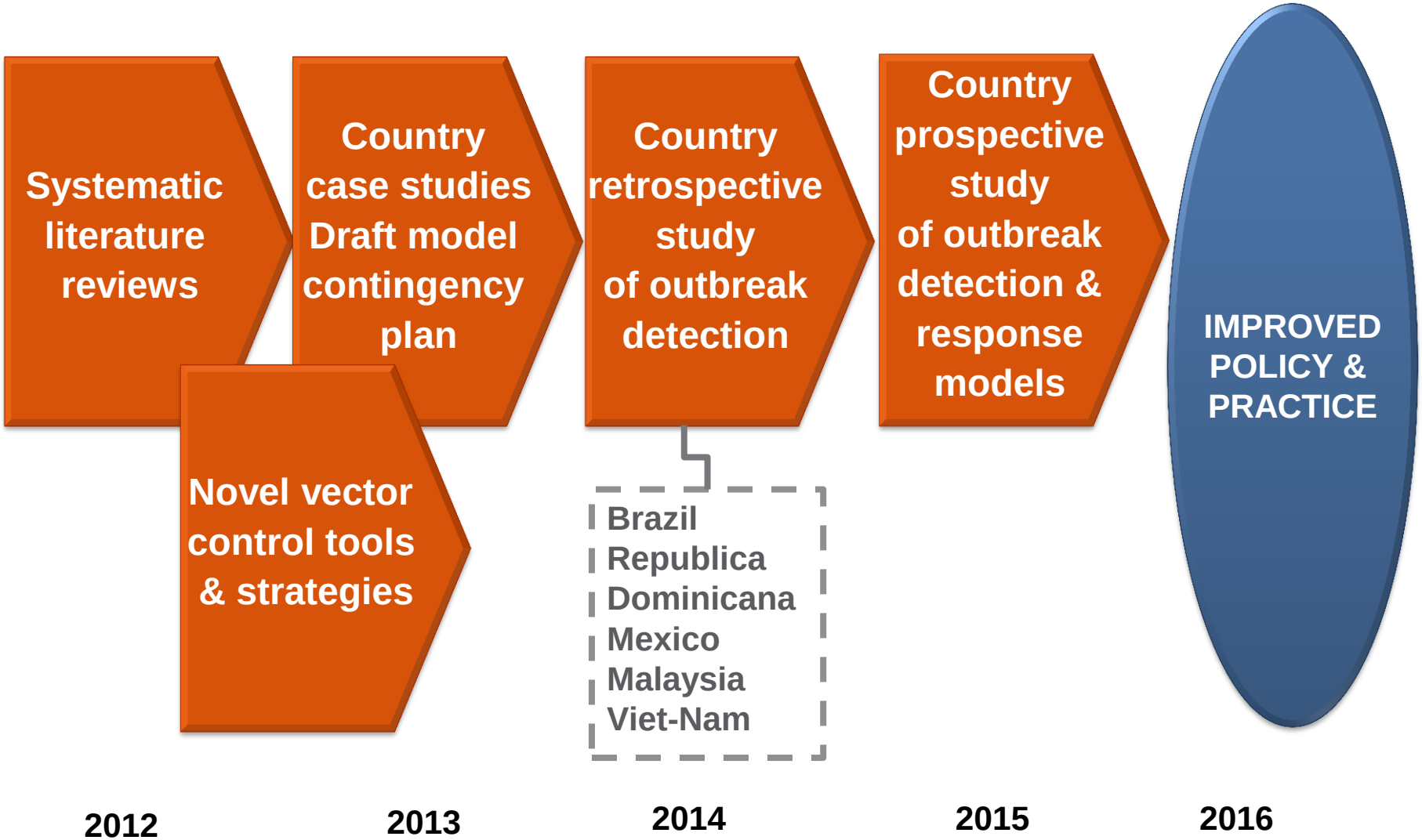
OUTBREAK DETECTION & RESPONSE

DENGUE OUTBREAK ANALYSIS

1. Indicators for triggering response?
2. Early warning signs of outbreak?
3. Passive and active surveillance: what is affordable?
4. Epidemic response: a structured approach

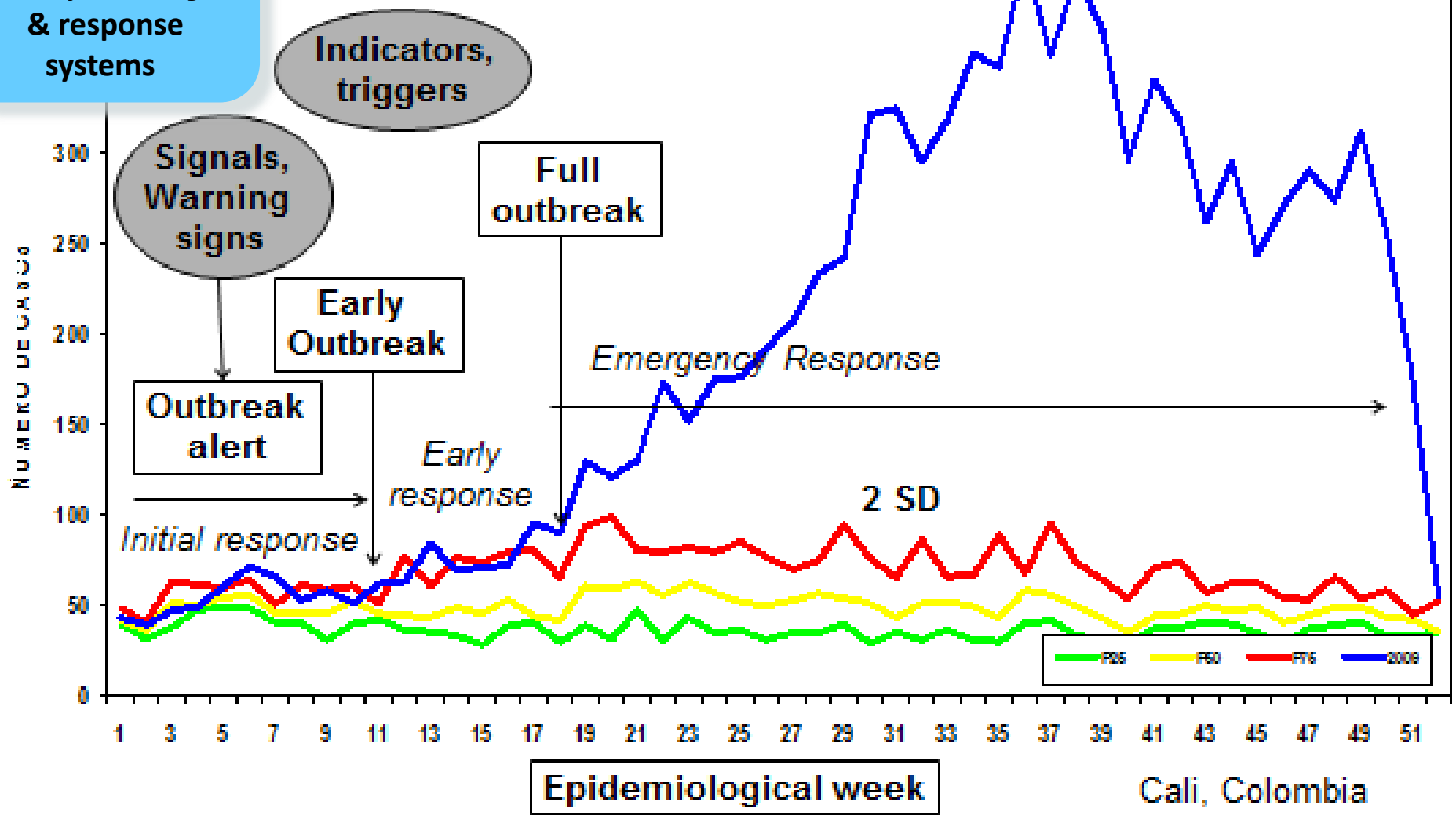


IDAMS WP3 STRUCTURE



PHASES AND INDICATORS OF A DENGUE OUTBREAK

Towards effective & affordable early warning & response systems



RETROSPECTIVE & PROSPECTIVE STUDY OF NEW OUTBREAK DETECTION & RESPONSE MODEL(S)

- Identification of candidate alarm signals for outbreaks
- Retrospective testing of candidate alarm signals and lap times (between signal and outbreak)
- Evidence based definition of «dengue outbreak»
- Testing effective vector management during outbreaks
- Development of tool box for dengue contingency planning
- Prospective testing of the tool box

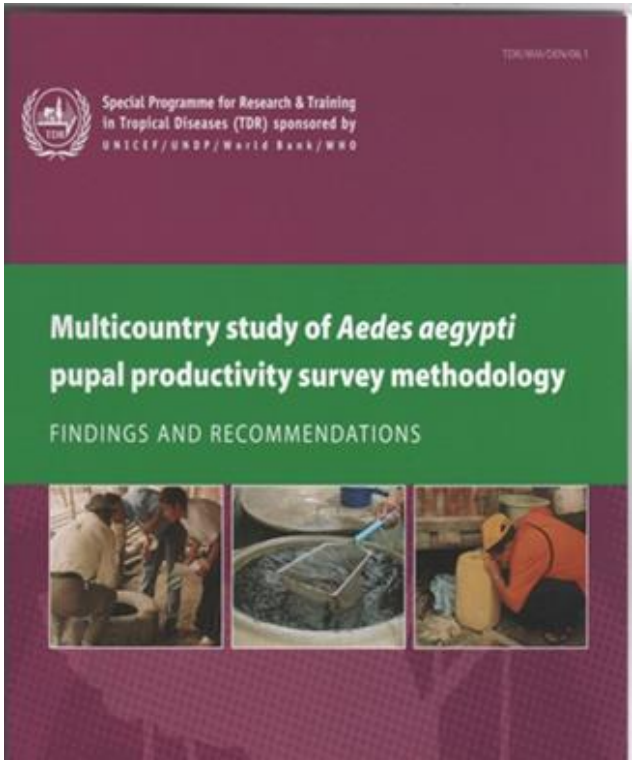
VECTOR CONTROL

- TARGETED INTERVENTIONS
- COMMUNITY-BASED ECO-SYSTEM MANAGEMENT
- ENTREPRENEURSHIP

RESEARCH ON IMPROVED AND INNOVATIVE DENGUE VECTOR CONTROL I

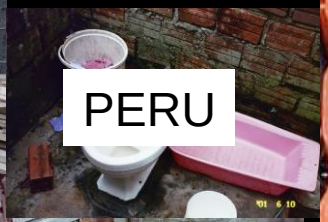
- Multi-country research study on targeted productive containers (2006-2008)
  - **Comparative multi-country research in Mexico, Peru and Venezuela** as well as in Kenya, Myanmar, Philippines and Thailand

➡ *Routinely used "larval surveys" to determine the presence or absence of dengue vectors should be complemented by annual or biannual "pupal productivity surveys" during the wet season in order to* ***identify "productive container types" for targeted interventions***



KENYA

Categories



PERU

MEXICO

MYANMAR

THAILAND

VENEZUELA

PHILIPPINES

VIETNAM

RESEARCH ON IMPROVED AND INNOVATIVE DENGUE VECTOR CONTROL II

- **Innovative Community-based Ecosystem Management Interventions for Improved Dengue Disease Prevention in five urban settings of Latin America - TDR/IDRC Canada research initiative (2010-2014)**
  - **Phase I**: Ecological, biological and social ("eco-bio-social") situation analysis in five urban settings leading to partnership-driven community-based intervention design
  - **Phase II:** Intervention research (Cluster Randomized Trials, CRT, accompanied by participatory social research) – Analysis being concluded and publications)

Research site	Social-ecological setting	Community intervention approach	Vector control approach
Brazil	City of Fortaleza (population 2,447,409)	Community, municipality	Small disposable containers, clean up programme with community Elevated tanks: develop lids (to replace continuous larviciding) with agents
Colombia	Municipality of Girardot (Population 132,456, population density 700/km2)	Community, municipality, schools	ITN curtains (1st step) ITN water container covers (2nd step) to protect productive containers (wash basins & ground tanks) involving entomol technicians & community
Ecuador	City of Machala (population 281,500)	Public health agents, Vector control agents, community representatives, municipality (solid waste collection)	Barrels/drums: locally adapted covers Small dispos. containers: clean up; waste management with communities, schools, Inspectors (PH and vector control)
Mexico	Acapulco, specifically Ciudad Renacimiento (population 48,460)	Community, health workers, educational workers, parents representatives in schools	Buckets,pots: clean up with community wash basins: ITN cover locally manufactured ITN window screens (locally manufactured)
Uruguay	City of Salto (population 123,000 inh.)	Municipality, schools, community	Campaign type interventions during 3 months of potential transmission including clean up (acc. to productive containers) with municipality agents. Ecosystems observatory for early warning

RESEARCH ON IMPROVED AND INNOVATIVE DENGUE VECTOR CONTROL II

Quintero *et al. BMC Infectious Diseases* 2014, **14**:38
http://www.biomedcentral.com/1471-2334/14/38

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Ecological, biological and social dimensions of dengue vector breeding in five urban settings of Latin America: a multi-country study

Juliana Quintero[1*], Helena Brochero[2], Pablo Manrique-Saide[3], Mario Barrera-Pérez[4], César Basso[5], Sonnia Romero[6], Andrea Caprara[7], Jane Cris De Lima Cunha[8], Efraín Beltrán - Ayala[9], Kendra Mitchell-Foster[10], Axel Kroeger[11], Johannes Sommerfeld[12] and Max Petzold[13]

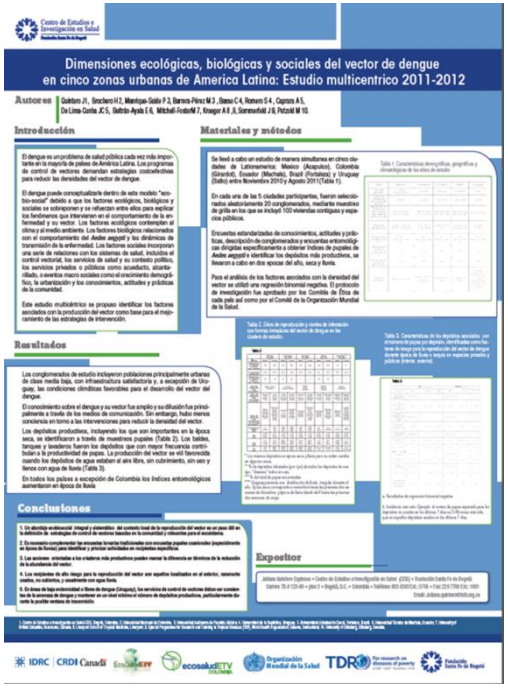


Table 4 Breeding places and infestation levels with immature dengue vectors in clusters

	Mexico (n = 20)		Colombia (n = 20)		Ecuador (n = 20)		Brazil (n = 10)		Uruguay**** (n = 20)	
Season	**Dry**	**Wet**	**Dry**	**Wet**	**Dry**	**Wet**	**Dry**	**Wet**	**Dry**	**Wet**
Private water containers per cluster	728	603	184	263	443	582	445	927	54	47
% outdoor containers	92.4	97.2	85.2	79.6	76.3	52.3	24.1	25.3	79.4	84.3
Number of Public containers per cluster	16	19	13	35	4	2	30	35	1	1
Most frequent container types*	Buckets, barrels, wash tanks		Wash tanks, barrels, buckets		Buckets, cans, wash tanks		Tires, barrels, buckets		Buckets, wash tanks	
Container types most frequently with larvae**	Tank 1.6% Barrel 1.3%	Can 19.1% Tire 15.0%	Can 44.1% Small cont. 34.3%	Tire 54.1% Tank 27.5%	Tank 21.7 Flower vase 20.8%	Tire 39.6% Tank 27.9%	Tire 7.1% Small cont. 1.7%	Nat. Prod 16.7% Tire 8.3%	Pot 60% Small Cont. 7.7%	Pot 70.6% Tire 55.5%
Most productive container types (% of all pupae)***	Bucket 34.5% Barrel3 0.6% Tank 23.1%	Small used 25.4% Bucket 21.0% Barrel 18.1% Cans 14.2%	Tank 71.2% Barrel 24.1%	Tank 72.5% Barrel 8.9% Tire 6.1%	Tank 47.9% Bucket 22.6%	Tank 35.5% Tire 15.9% Small Cont. 13.9% Cans 9.4%	Small cont. 50.9% Barrel 29.1%	Barrel 36.4% Cans 32.5% Bucket 8.0%	Barrel 65.3% Cans 34.7%	Cans 29.9% Others used 15.4% Bucket 13.9% Barrel 12.1%
Number of pupae per cluster, rounded (with CIs)	13 (6–20)	83 (53–112)	465 (270–661)	390 (293–488)	146 (97–195)	576 (419–734)	6 (0.6- 10.4)	54 (25–82)	4 (0–7.6)	20 (8–32)
PPI (CIs)	0.03 (0.01- 0.05)	0.2 (0.14- 0.26)	1.24 (0.73- 1.75)	1.03 (0.81- 1.25)	0.37 (0.25- 0.49)	1.42 (1.02- 1.82)	0.01 (0.00- 0.03)	0.15 (0.07- 0.23)	0.01 (0.00- 0.03)	0.07 (0.03- 0.11)
PPH (CIs)	2.4 (1.24- 3.64)	18.1 (12.8- 23.4)	296.1 (82.8- 510.0)	213.3 (103–323.7	35.0 (12.7- 57.2)	150.2 (68.1- 232.3)	1.8 (0.27-3.37)	29.7 (9.1- 50.3)	0.32 (0.00- 0.66)	1.7 (0.76-2.61)
BI (CIs)	5.5 (3.5- 7.3)	29.2 (23.6- 34.8)	29.2 (24.5- 33.8)	39.8 (33.5- 46.0)	32.9 (28.0- 37.8)	57.9 (48.6- 67.2)	3.3 (1.7- 4.8)	9.6 (5.9- 13.3)	0.7 (0.27- 1.06)	6.2 (4.0-8.5)

*The same water tanks in the dry and wet season, but rank order has changed in some cases.
% of infested containers (of specific type) from all containers of that type; "small containers" were all un-used . *% of all pupae encountered **** Uruguay has an irregular distribution of rainfall during the year; dry season corresponds to November until first two weeks in December and wet season to April until the first two weeks of May.

RESEARCH ON IMPROVED AND INNOVATIVE DENGUE VECTOR CONTROL III

- **Multi-disciplinary research teams in Brazil (Fortaleza), Colombia (Girardot), Ecuador (Machala), Uruguay (Salto)**

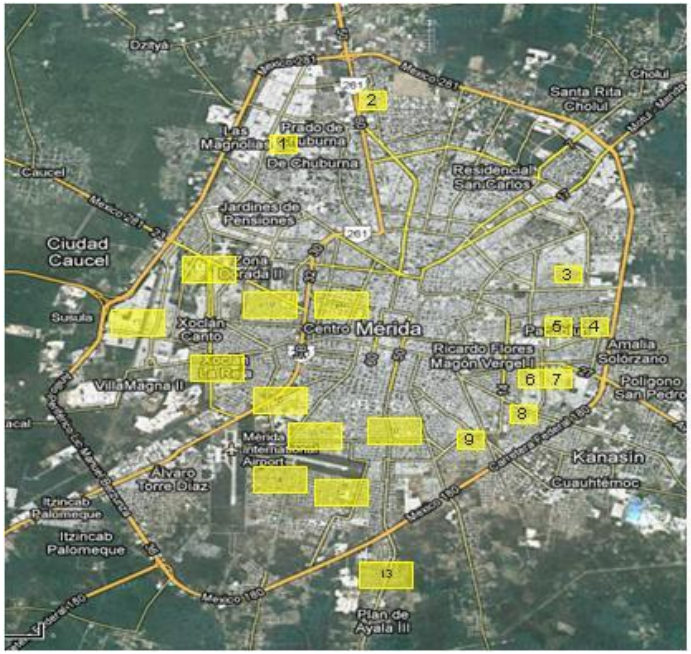
- (Local) development and testing of new and innovative dengue vector control tools
- New strategies of empowering communities
- Strengthened community involvement and interaction of community representatives with control services , municipalities and other public actors
- Impact on vector densities

Photos: Team Dr Carraquilla (PI), Colombia

Recycling and backyard cleaning scheme, Fortaleza, Brazil, Photo: Dr Caprara (PI), University of Ceara Stata

RESEARCH ON IMPROVED AND INNOVATIVE DENGUE VECTOR CONTROL III

- Innovative Community-based Ecosystem Management Interventions for Improved Dengue Disease Prevention in five urban settings of Latin America - TDR/IDRC Canada research initiative
  - **Phase III: Scaling up of proven interventions at city levels, supported by national control programmes in Brazil, Colombia and Mexico (planned for 2014-15)**



LISTADO DE COLONIAS

1. Francisco de Montejo
2. Cordemex
3. Polígono 108
4. Fidel Velázquez
5. Pacabtún
6. Vergel II
7. Vergel III
8. San Antonio Kaua
9. Unidad Morelos
10. Cinco colonias
11. Castilla Cámara
12. San José Tecoh
13. Plan de Ayala sur
14. San Antonio Xluch
15. Manzana 115
16. Mulsay
17. Juan Pablo II
18. Yucalpeten
19. Bojórquez
20. Centro

Photos: Research Team Dr Manrique, University of Yucatan (UADY)

RESEARCH ON IMPROVED AND INNOVATIVE DENGUE VECTOR CONTROL III

- New TDR research activity on Social Enterprise Innovation and Social Entrepreneurship (2014-…)
  - **Planned case study research on R&D, health service delivery and other public health schemes, including innovative vector control technologies through social enterprise models**
  - **Potentially new and innovative production and service delivery models for community-based vector control and other "green" technologies**

Local production of curtains
Colombia, Photo: Team Dr Carrasquilla (PI)

FACILITATE INNOVATION IN DENGUE DRUG R&D:

B Canard, Antiviral research and development against dengue virus

http://www.who.int/tdr/research/ntd/dengue/dengue_full_length_report.pdf

(needs updating)

OUTLOOK

Possible areas of future joint actions in the Americas – for discussion:

- Meeting with country surveillance staff on reporting using revised dengue classification using ICD codes
- Research on warning signs for severe dengue
- Burden of disease studies
- Meeting with country surveillance staff on early outbreak detection, response and reporting
- How to foster/favour innovation in dengue drug R&D
- Others …

THANK YOU FOR YOUR ATTENTION
GRACIAS POR VUESTRA ATENCIÓN
OBRIGADO PELA VOSSA ATENÇÃO