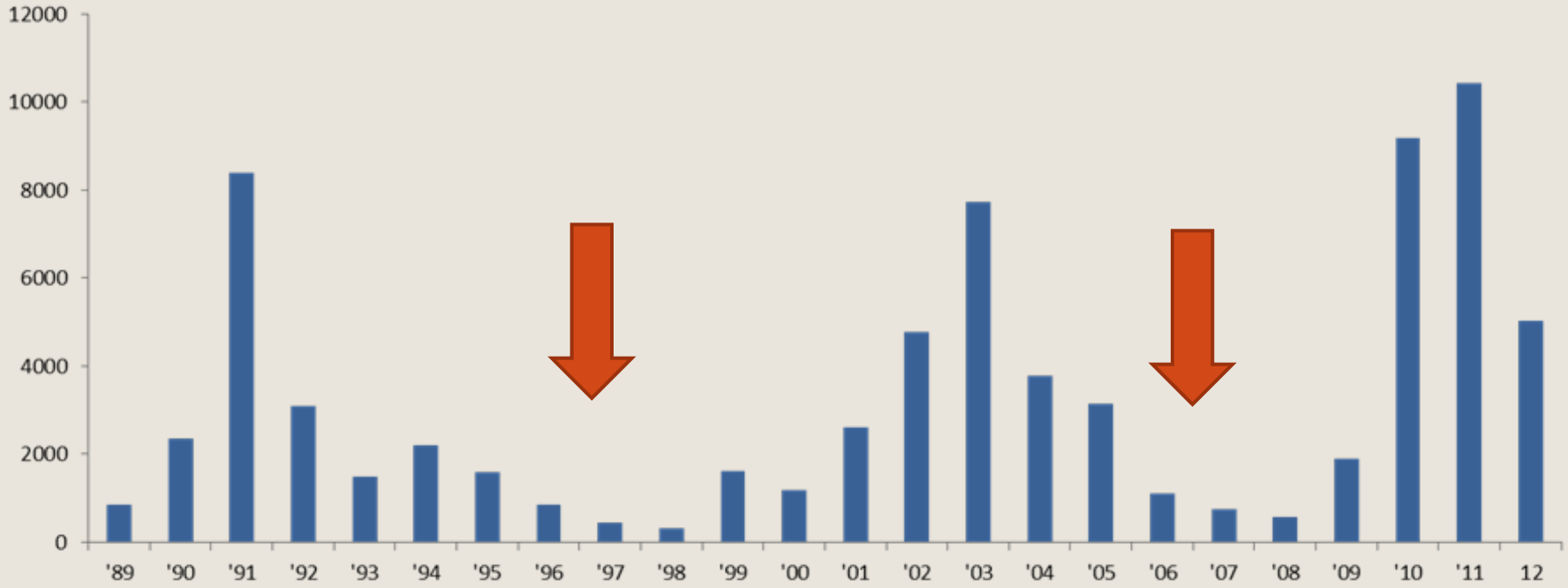
A global approach to combat Visceral Leishmaniasis

J. Alvar

Drugs for Neglected Diseases *initiative*



EDCTP, Berlin 30 June 2014

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Outline

VL, a general overview of needs

- Impact and progress made
- From patient needs to public health perspective: PKDL, Contacts, Asymptomatic carriers

VL as WHO R&D demonstration project

- Concept
- Objectives

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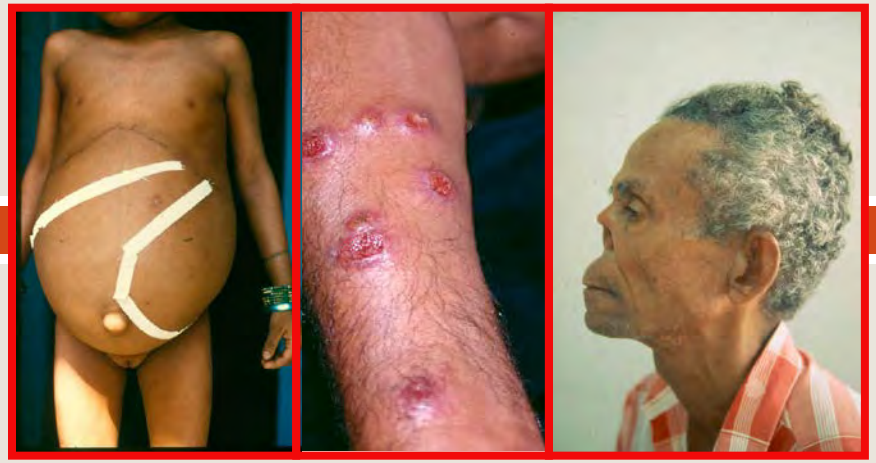
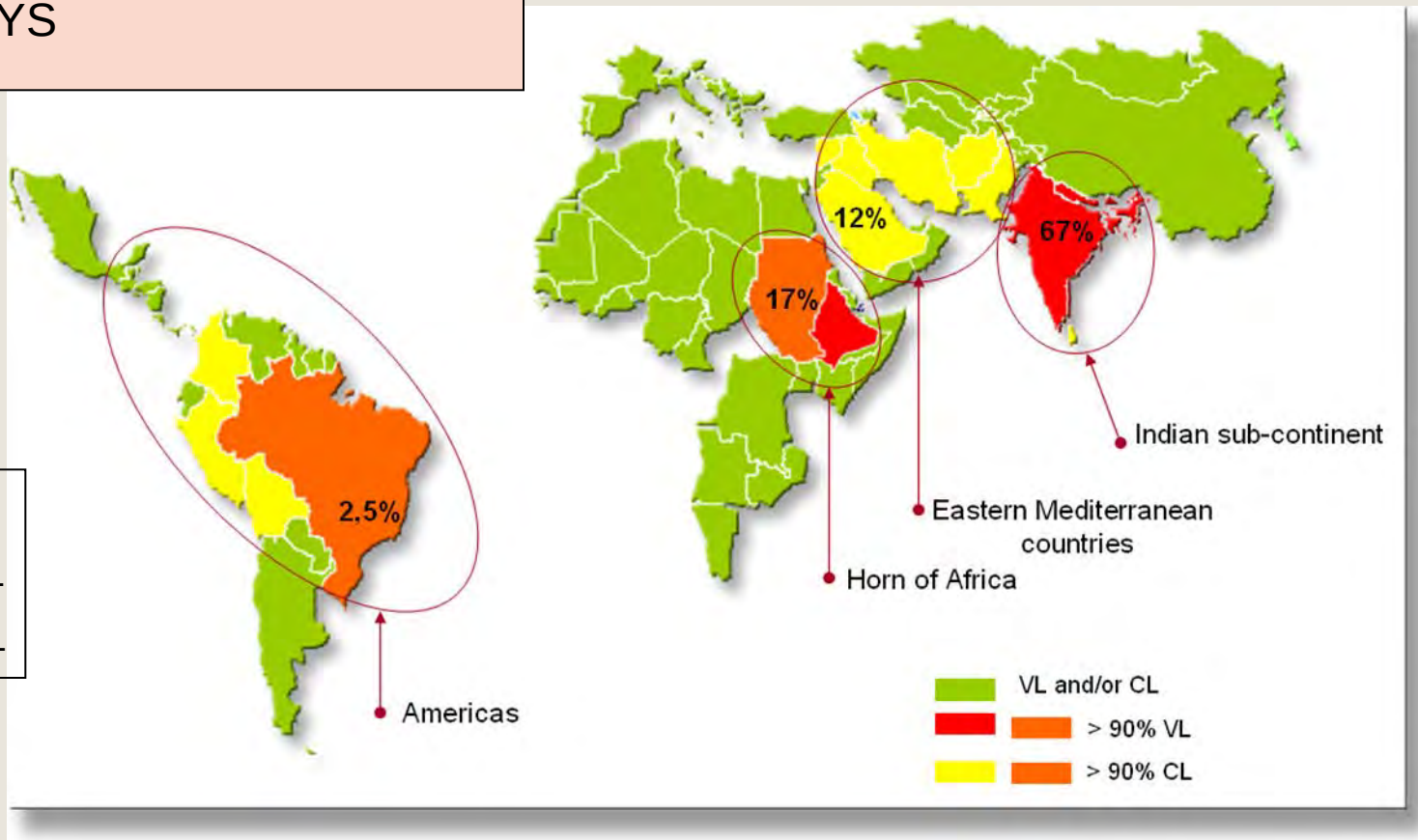
Leishmaniasis



- VL & CL (MCL, DCL, PKDL, LR, HIV/VL)
- 98 endemic countries
- Incidence: 0,4 M VL, 1,2 M CL cases/yr
- 2,35 million DALYS



VL and/or CL
> 90% VL
> 90% CL

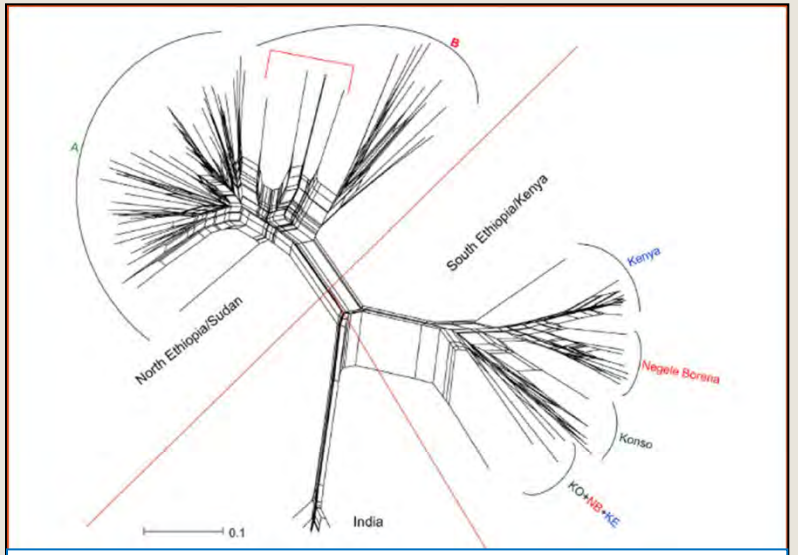
Pitfalls in chemotherapy: the African case

Drugs	SSG	Ampho B Liposomal	Ampho B deoxycholate	MIL	PM sulphate	SSG+PM	LAB+SSG	LAB+MIL	PM+MIL
Clinical efficacy									
Asia	35-95% (depending on areas)	> 97% all regions	> 97%; single dose: > 96%	94-97% (India)	94% (India)	Not documented	> 97%	> 97%	> 97%
Africa	93%	33 - >97% (depending on areas)	Not fully established	72%	84%	91%	87%	79%	Not documented
Resistance	As high as 60% (India)	Not documented	Not documented	20% (Nepal)	Lab isolates (easily)	Lab isolates (easily)	Lab isolates	Lab isolates	Lab isolates (easily)

Table 2. Cure (efficacy) at end of treatment and at 6 months after treatment.

	SSG	PM	P*†
• Um el Kher, Sudan	14/17 (82.4%)	4/28 (14.3%)	<0.001
• Kassab, Sudan	14/15 (93.3%)	7/15 (46.7%)	0.014
• Kenya	15/15 (100.0%)	12/15 (80.0%)	0.224
• Gondar, Ethiopia	37/40 (92.5%)	30/40 (75.0%)	0.066
• Arba Minch, Ethiopia	27/29 (93.1%)	28/29 (96.6%)	1.000
P*‡	0.568	<0.001	

Hailu PLoS NTD 2010



Gelenew PLoS NTD 2010

VL, elements fuelling transmission

Interlinked contexts with poorly described infection sources driving disease manifestation and outbreaks on top of a complex social, nutritional and immune picture

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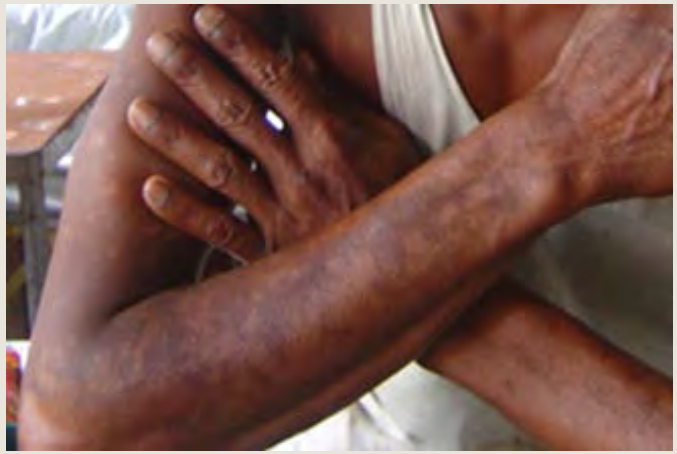
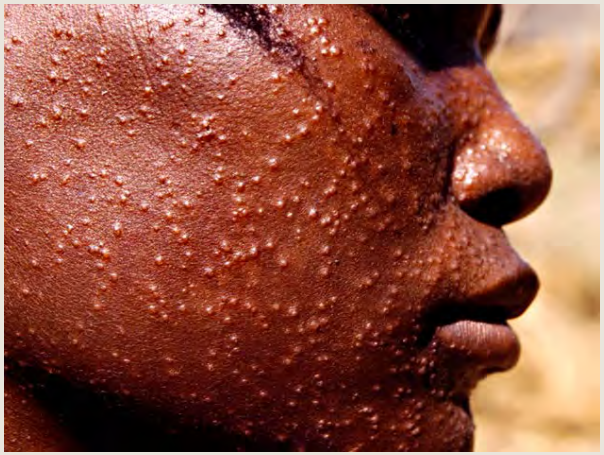
Post Kala-azar Dermal Leishmaniasis (PKDL)

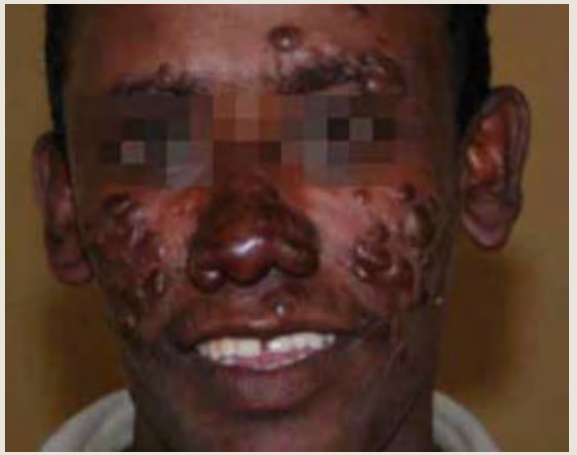
An immune mediated process: VL (Th2) - PKDL (Th2/Th1) - cure (Th1)



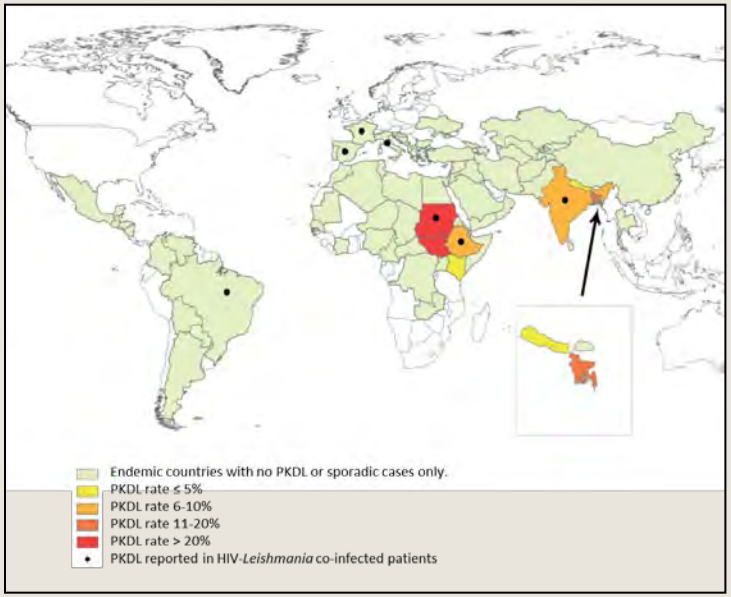
macular



papular



nodular



Main clinical differences	**Sudan**	**India**
Most common presentation	polymorphic, papular	monomorphic, macular
Typical distribution (face-arms/chest-legs)	yes	often not
Spontaneous cure	yes	no
May occur while on Rx for VL	yes	no
Genital lesions	uncommon	common

Zijlstra et al., Lancet ID, 2003

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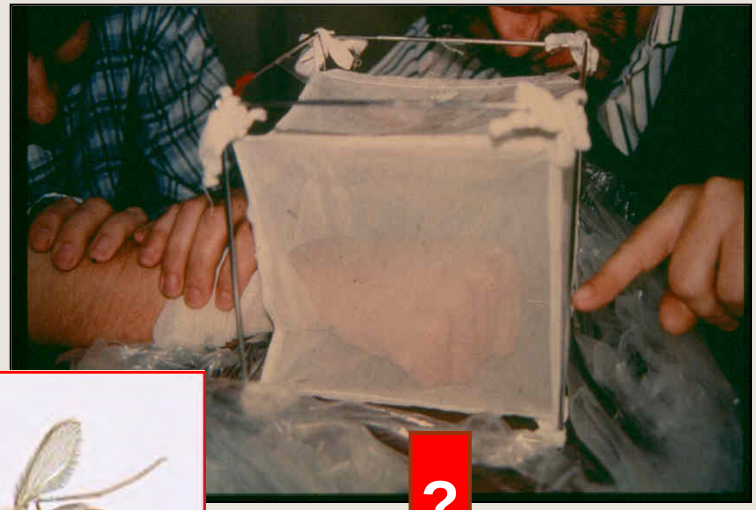
PKDL, epidemiology & infectivity

Hypothesis: PKDL patients do play a role in transmission

Objectives:

- To establish the burden of VL:PKDL at the village level
- To prove infectivity of PKDL patients according to forms
- Xenodiagnosis vs surrogate biomarker
- To provide recommendations for treatment, control, & surveillance



?

Recommendations by the Consortium on PKDL, 2013
Treatment & Pathogenesis

Africa: SSG 20 mg Sb^{5+}/kg IM/IV for 30–60 days
Asia: miltefosine, for 12 weeks daily 100 mg or 50 mg weighting ≥ 25 kg or <25 kg, respectively
AmBisome: 5 mg/kg per day IV, twice a week up to 30 mg/kg

- Pharmacokinetic of drugs targeting the skin
- Understand the pathogenesis by clinical forms and regions
- Randomized clinical trials of short course regimens
- Immuno-chemotherapy

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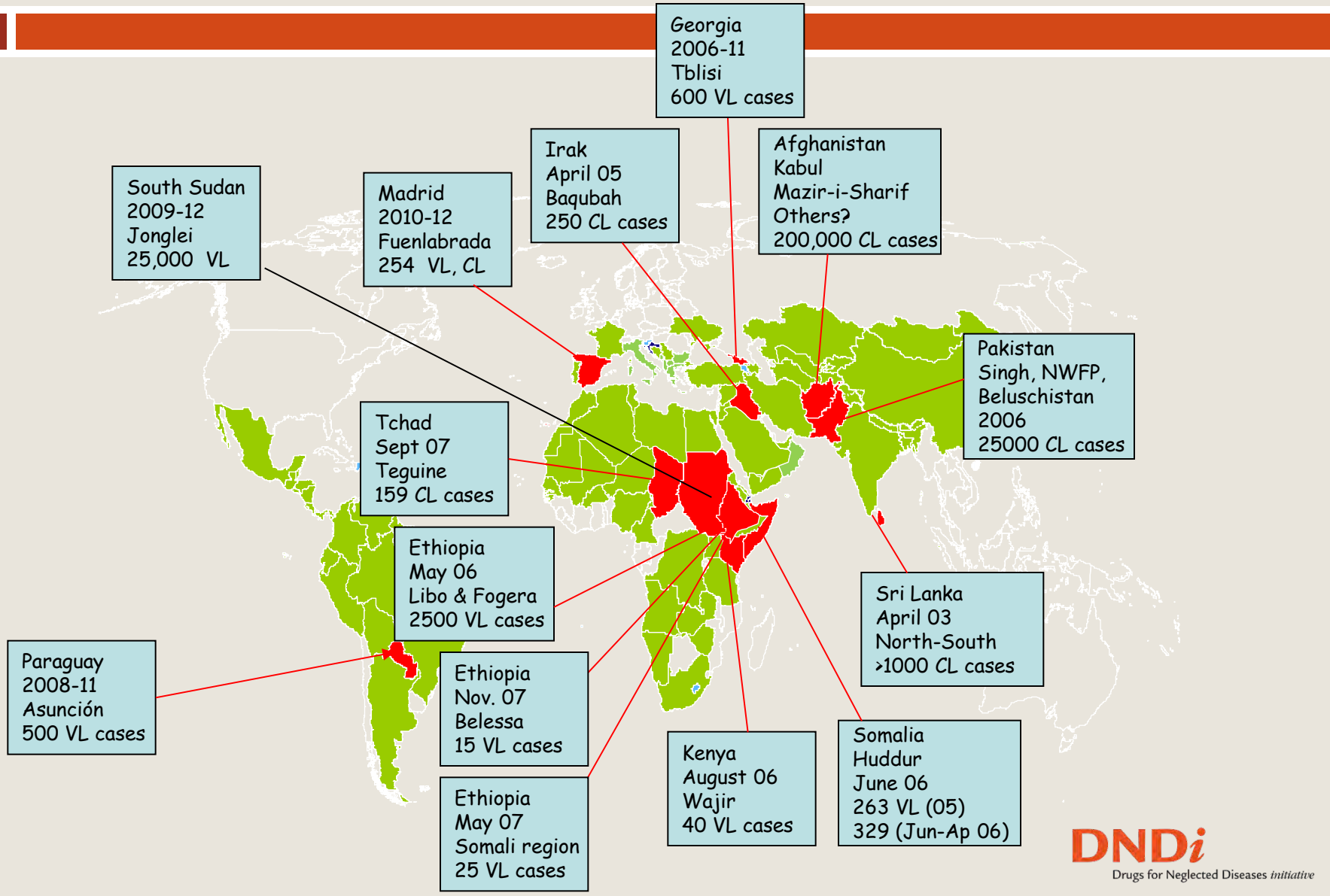
Major emerging foci & Outbreaks (2006-13)



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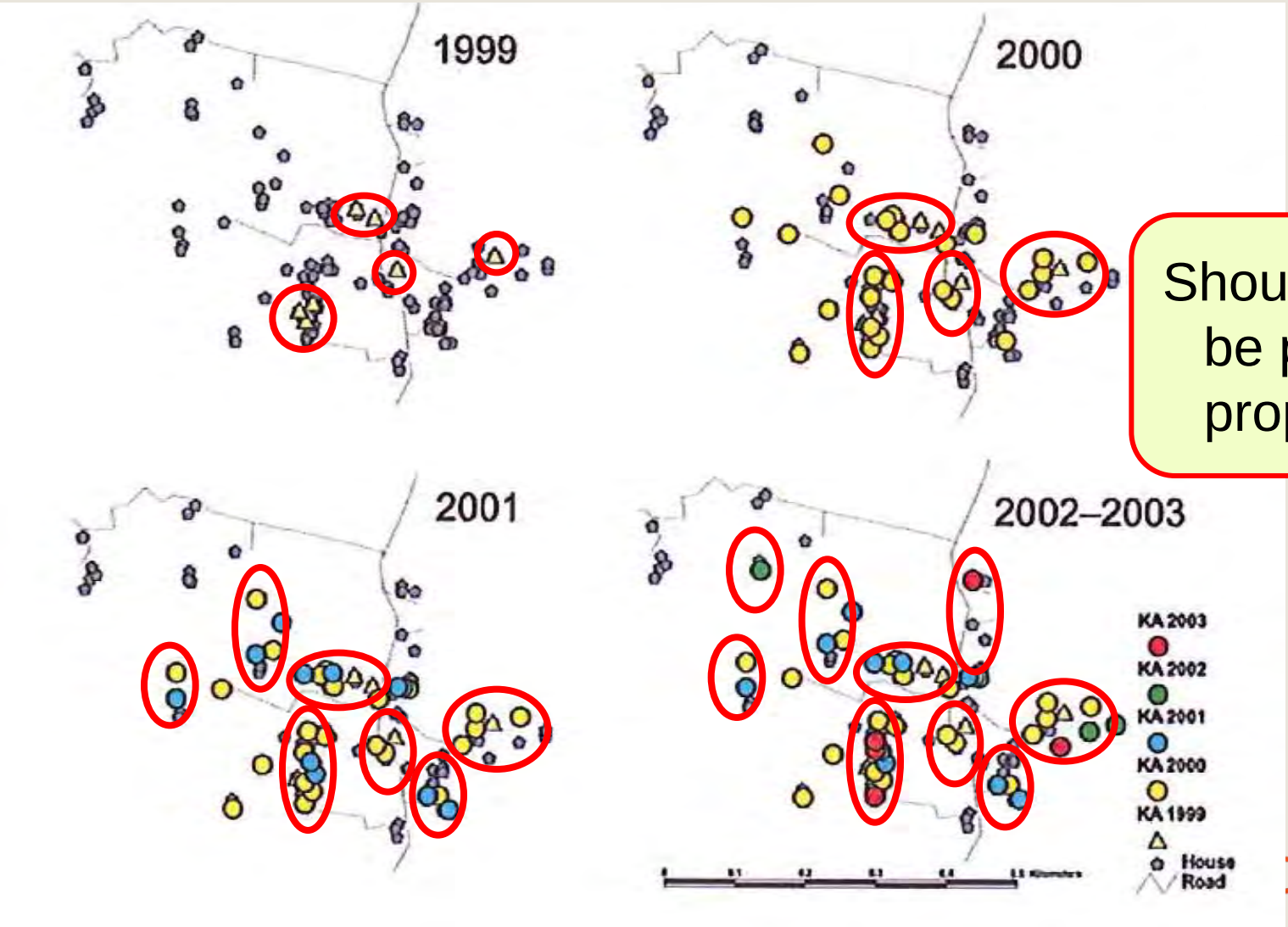
Contacts: VL cluster transmission by year of onset, Bangladesh (Bern et al., 2005)



Should contacts be put under prophylaxis?

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Asymptomatic infections

Importance

- 1:4 Kenya, Uganda 1:8, Spain 1:50
- Blood donors (Riera et al, TRSMH, 2004)
- Serological/PCR surveys (Topno et al, AJTMH, 2010):
  - From 21 sero + 17 were PCR +
  - From 313 sero - 2,5% were PCR +

Role of Infective asymptomatic dogs (Molina et al., TRSTMH, 1994)

Definition

- Serology
- PCR
- LST
- Cytokine environment

Are asymptomatic human carriers playing a role in transmission?

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Summary of main challenges

On going studies completed, bringing 1-3 new oral-combination treatments by 2018

African VL

- Develop Rx based in the parasite specifies

PKDL

- Infectivity by clinical forms
- Which PKDL patients need Rx, which Rx?

Contacts

- Develop (oral) drug to protect family members

Asymptomatic carriers

- Infectivity
- Develop oral drug as preventive chemotherapy for MDA

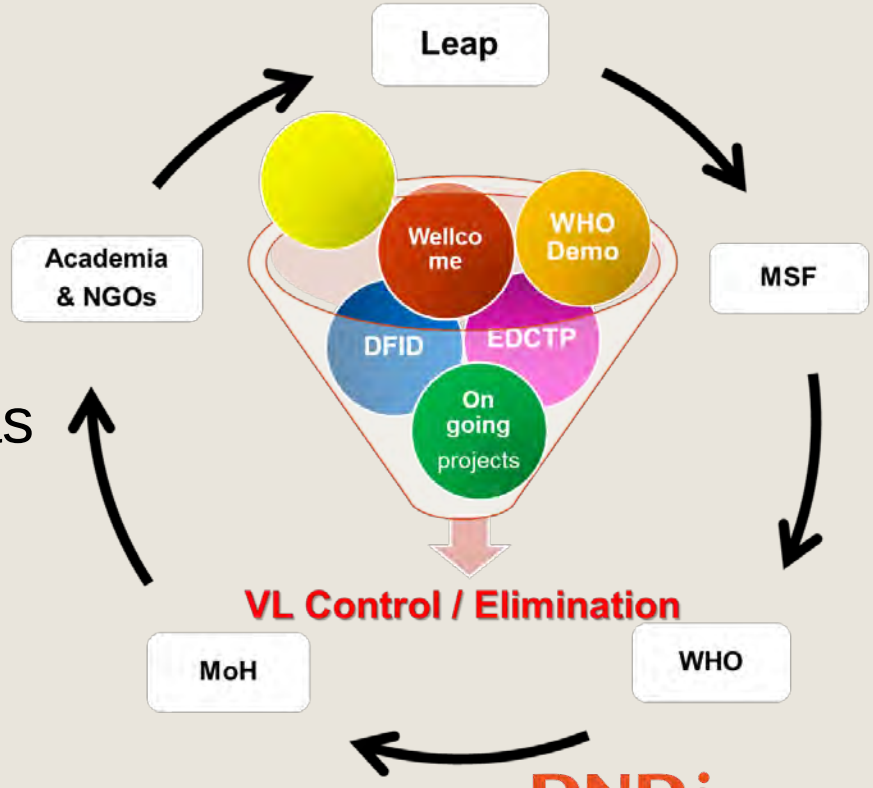
DND*i* is committed to move from drug development for treating individual patients to become aligned with the **London Declaration** contributing in the **control/elimination** of VL by 2020

…in the new landscape *London-2020*

Patients and implementation first…

… but fully committed in (de-)figthing leishmaniasis by:

- **Down stream research**
  - Fexi/miltefosine
- **Up stream research**
  - Oxaboroles, 2098
- **Innovation**
  - Open spaces, new Rx areas
- **Implementation**
  - Engaging with MoHs



Gracias

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Back up slides

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VL reported cases (average 2004-08) and estimates

	Cases reported/year	Estimated annual
America	3 661	5 000 to 7 000
West Africa	-	-
East Africa	8 569	30 000 to 40 000
Mediterranean	875	1 500 to 2 000
Middle East & Central Asia	2 496	5 000 to 7 500
Indian Subcontinent	42 619	160 000 to 320 000
	58 220	**201 500 to 376 500**

Alvar et al., PLOs One, 2012

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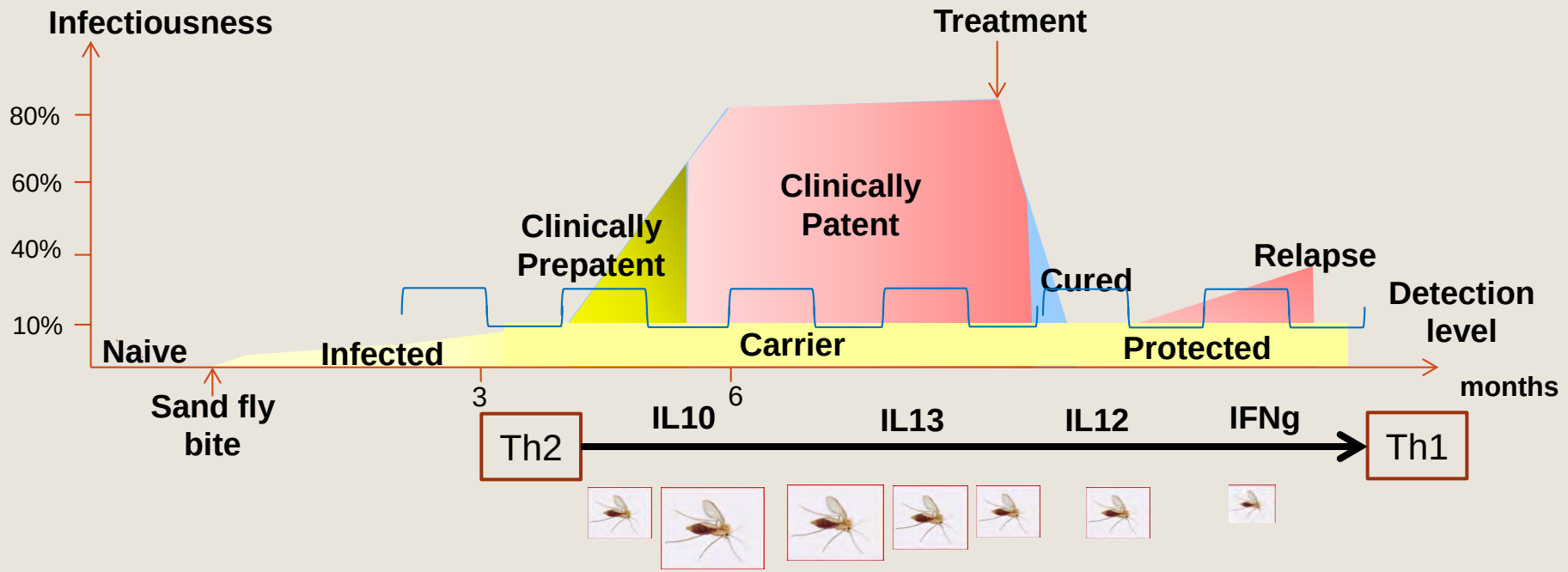
Hypothetical model of the natural history of infection & disease in leishmaniasis



CONDITION	IFAT	rK39	PCR	Culture	CPA	LST	IFNg	Infectivity
Infected	+	-	+/-	-	+	+	+	¿?
Prepatent	++	+	++	+	-	-	-	¿?
Asymp. carrier – Infectious	+	+	+	+/-	+	+	+	¿?
Asymp. - Protected	+/-	-	+/-	-	++	++	++	¿?
Cured (after TX)	+	+/-	-	-	++	++	++	-

Aims of the VL Program…

- In the Near Term
  - Register combinations for East Africa
  - Provide ammunition for policy change in India and LatAm
  - Determine suitability of miltefosine as an oral combination partner in East Africa
- Longer Term
  - Develop new oral drugs as quickly as possible by
    - New PoC paradigm
    - Increasing sites and recruitment rates
  - Upgrade LEAP to v2.0
  - Determine role of asymptomatics & PKDL patients as disease reservoir
  - Increase Discovery pipeline

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Challenges at the turn of the millenium

- Leishmaniasis sharing all characteristics of a typical poverty-related disease (NTD)

PLUS

- Lack of up dated information
- No visibility according to its burden
- Epidemiological complexity
- No concept on how to manage the disease
- No global strategy
- No political recognition
  - WHA Resolution 2007/60.13

Disease not under proper control

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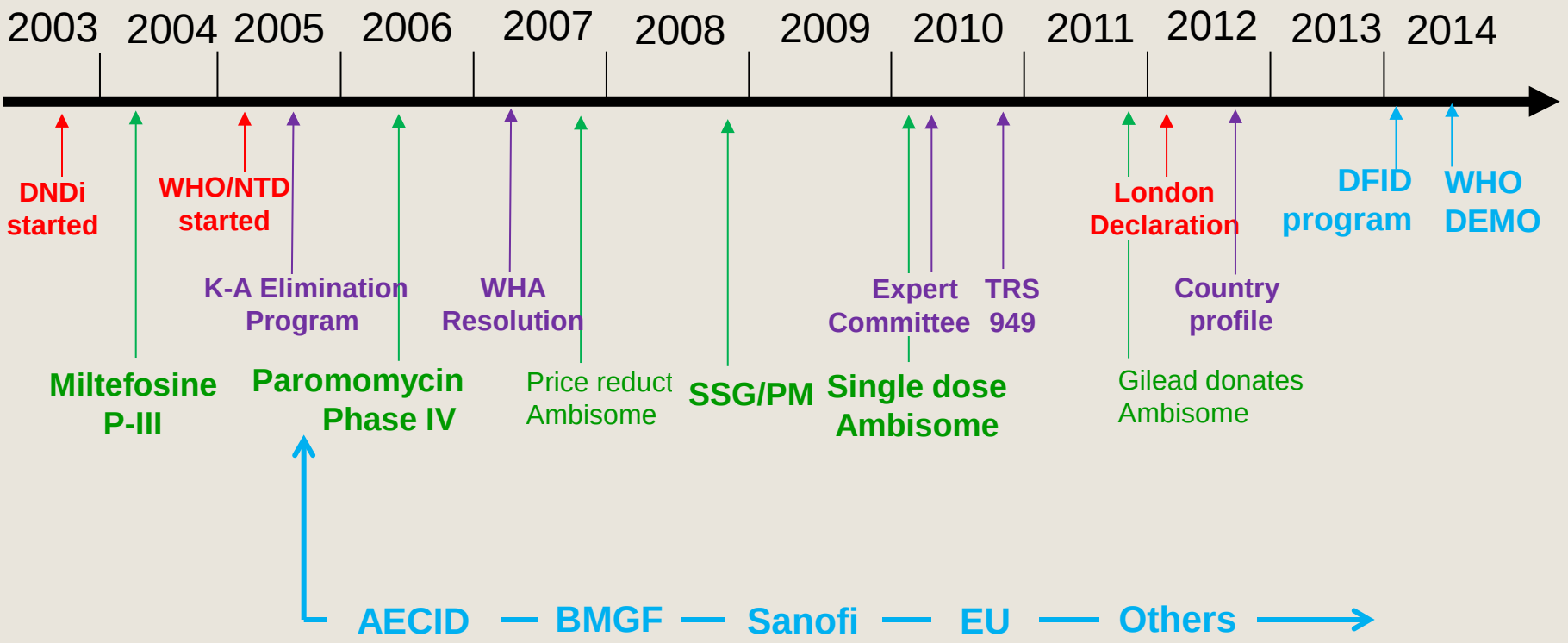
A productive decade for VL



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DNDi's VL portfolio

	<2011	2012	2013	2014	2015	2016	2017	2018
Africa								
Leap 0106 AmBisome		completed	Recomm. & Public.					
Leap 0208 Combo	Phase II	Last patient	Go/No Go Publication	PK MIL (allo) MIL/Fexi	Publicat. Phase II		completed	Public & Recomm.
Leap 0511 HIV/VL		Ph-III				completed	Public & Recomm	
Sudan Fexi			Ph-II		Go/No Go Ph-III		completed	Public. & Recomm.
SSG/PM PV			completed	Public. & Recomm.				
Asia								
Bangladesh Combo/LAB x 5			completed	Public. & Recomm.				
India feasibility/implement. Combo & LABx1 &LABx3		Ph-IV				completed	Public & Recomm.	
America								
Brazil Combo & LAB		Ph-II		completed	Public. & Recomm.			

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Asymptomatics

Transactions of the Royal Society of Tropical Medicine and Hygiene (2004) 98, 102–110

ELSEVIER

www.elsevierhealth.com/journals/trst

Detection of *Leishmania infantum* cryptic infection in asymptomatic blood donors living in an endemic area (Eivissa, Balearic Islands, Spain) by different diagnostic methods

C. Riera[a,*], R. Fisa[a], M. Udina[b], M. Gállego[a], M. Portus[a]

Table 1 Results of the different diagnostic methods applied in 122 blood donors: sensitivity of the several techniques

Blood donors		No. of blood donor positives/No. of blood donors studied					
Total studied	Infected[a]	Serology		DTH[c]	Nested-PCR	Culture	
		ELISA	WB			PBMC	BC[c]
122	36	7/122	14/122	15/67[c]	21/67	0/67	3/67[c]
		7/36	14/36	15/30[c]	27/36	0/36	3/30[c]
Sensitivity of the technique[b]		*19%*	*39%*	*50%*	*75%*	*0%*	*10%*

[a] We consider as probably infected those donors that tested positive on at least one of the techniques assayed.
[b] Sensitivity = no of donors positives/no of donors probably infected.
[c] Sensitivity of DTH and BC culture tests was calculated on 30 donors considered as probably infected (30 of the 67 screened).

Am. J. Trop. Med. Hyg., 83(3), 2010, pp. 502–506
doi:10.4269/ajtmh.2010.09-0345

Asymptomatic Infection with Visceral Leishmaniasis in a Disease-Endemic Area in Bihar, India

Roshan K. Topno,* Vidya N. R. Das, Alok Ranjan, Krishna Pandey, Dharmender Singh, Nawin Kumar, Niyamat A. Siddiqui, Vijay P. Singh, Shreekant Kesari, Narendra Kumar, Sanjeev Bimal, Annadurai Jeya Kumar, Chetram Meena, Ranjeet Kumar, and Pradeep Das

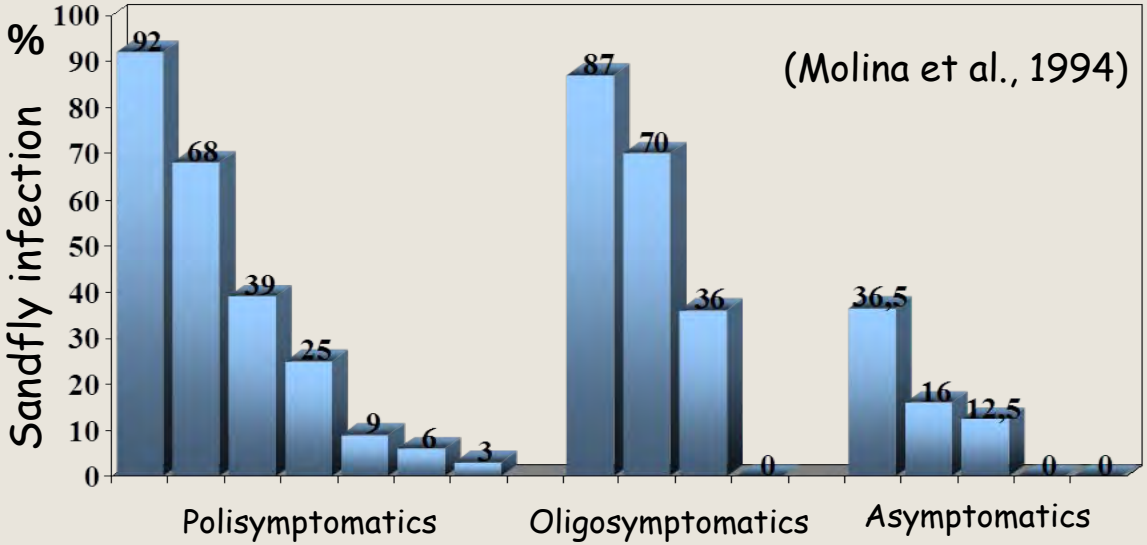
TABLE 2

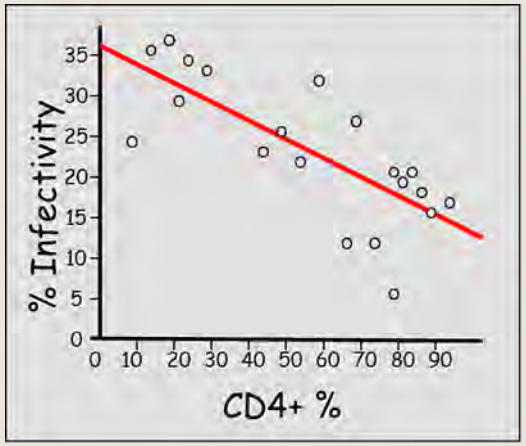
Comparative results of rK-39, PCR, and DAT among screened population at baseline survey, Bihar, India*

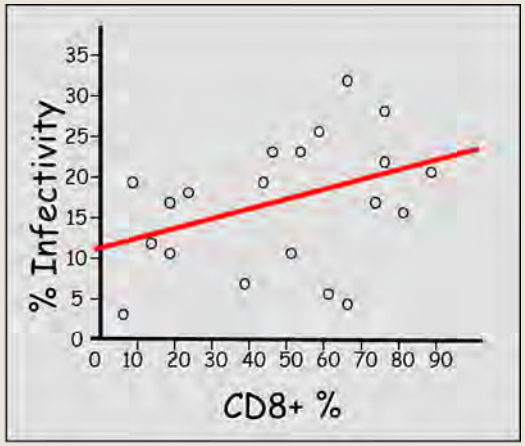
		PCR		
DAT	rK-39	No. positive	No. negative	Total
Positive	Positive	17	4	21
	Negative	3	15	18
	Total	20	19	39
Negative	Positive	0	3	3
	Negative	8	305	313
	Total	8	308	316

* PCR = polymerase chain reaction; DAT = direct agglutination test.

Dogs Infectivity to *Phlebotomus perniciosus*







(Guarga et al., 2000)

ative

Demonstration Project – WHO process

- 5-year project; Budget: 35 M €
- Research, clinical trials and access in 4 continents: **cross-regional** operationnal activities through collaborative coordination
- **Multiples partners**: MoH, Research Institutes, WHO, pharmaceutical partners etc.
- **Political and financial involvement of countries** (endemic countries, traditional and new donors countries); Looking at **Pool funding mechanism.**
- **Next steps: Implementation.**
- Report to the WHA on initial outcomes;
- **Global debate on sustainable financing and coordinating framework.**

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Visceral Leishmaniasis Demonstration Project – Guiding principles

Guiding principles of the Initiative:

- **Sharing knowledge and open innovation:** The establishment of a **Drug Booster Consortium as an open knowledge platform** would be a key asset to speed up upstream research, avoid duplication of research and decrease cost of R&D. Partners within the Drug Booster would agree **to screen their libraries together**, increasing the chance **to identify hits for later optimization.**
- **Exploring innovative incentives mechanisms:** The Initiative would explore innovative mechanisms such as a milestone prize for xenodiagnoses and quantitative PCR.
- **Equitable access**: To ensure **affordable access**, the Initiative would emulate collaboration with industrial partners similar to that between DND*i* and Sanofi for fexinidazole, a new drug being tested against the disease. Such agreements would make available, as **public goods**, any new therapeutic and diagnostic tools developed, as well as making them **available at affordable prices**.

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Visceral Leishmaniasis Demonstration Project – Guiding principles

- **Sustainable funding:**

a) New funding mechanisms**, such as a pool funding;**

b) **The European and Developing Countries Clinical Trials Partnership (EDCTP 2)**

c) **Innovative Medicines Initiative (IMI)**

d) contributions from **emerging-economy countries** and regions affected by the disease (Brazil, India, Middle East and North Africa)

e) **prizes**.

- **Coordination through cross regional collaborative approach**: The VL Global R&D & Access Initiative would be set-up in partnership with the existing VL consortia and research platforms from the different relevant regions.

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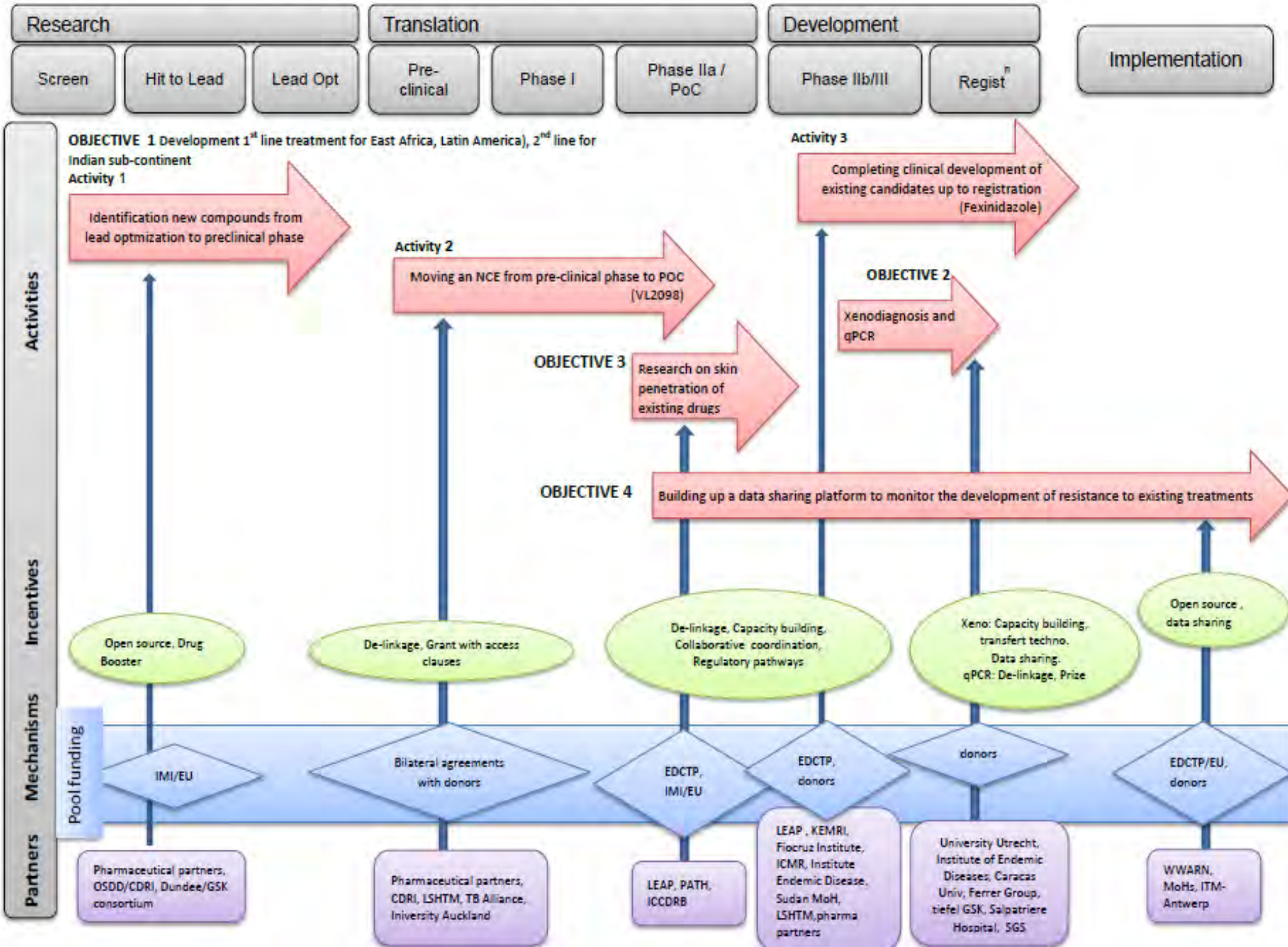
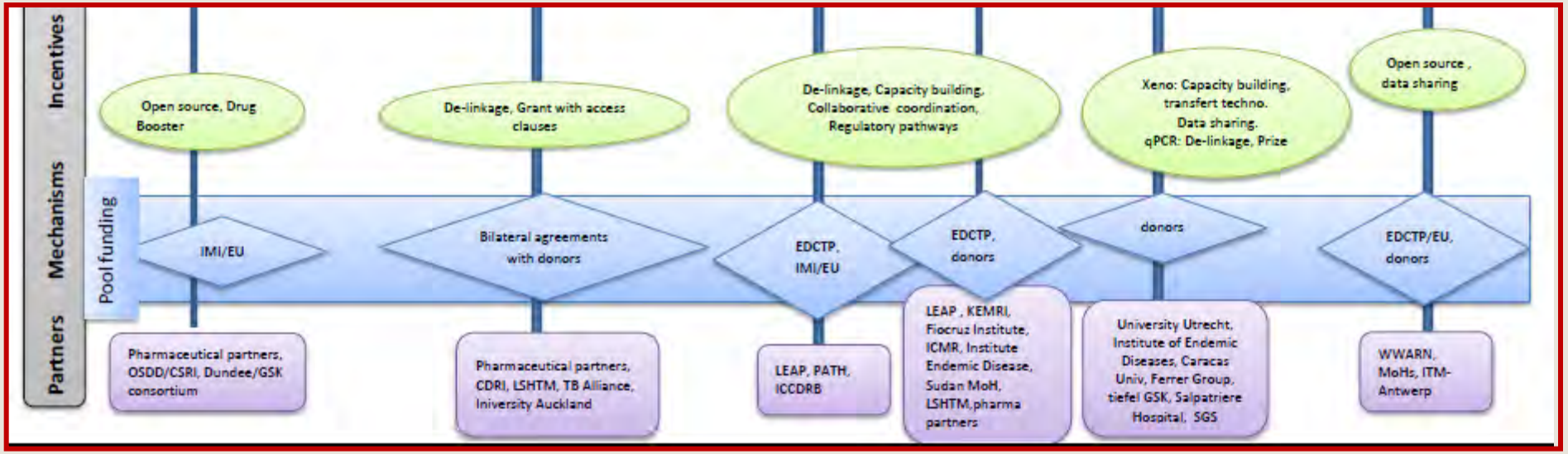
VL Global: Activities, Incentives, Mechanisms, Partners



VL demonstration project
Funding & Incentives mechanisms & Partners



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Next steps: towards implementation & demonstration

WHO process: pilot innovative mechanisms to finance and coordinate Health R&D; Induces transparency (cost etc).

Need on-going political and funding support from MSs from all regions: AFRO, SEARO, EMRO, EURO, PAHO, WPRO

Coordination and partnerships with partners for the implementation: LEAP, KEMRI, pharma, Academics, MoHs, etc.

Outcome of WHO Stakeholders' meeting in Geneva
Project plan and funded budget
Report to MSs at next WHAs on mid-term outcomes
Link with parallel debate on CEWG Follow-up: Financing and Coordination and Health R&D Observatory

Visceral Leishmaniasis Demonstration Project - WHO

- **DNDi VL Global Research & Access Initiative**, selected by EMRO, AFRO and initially supported by Sudan, France, Switzerland, Spain
- Demonstrate that Health R&D can be **boosted** through:

  a) **collaborative cross-regional coordination**,

  b) **innovative and sustainable approaches for R&D** (open innovation and IP management),

  c) **innovative sustainable financing mechanisms** (i.e: pool funding)
- **Guiding principles/CEWG**: Sharing knowledge and open innovation; Equitable access; Sustainable funding; Exploring innovative incentives mechanisms; Coordination through collaborative approach.

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VL as WHO R&D demonstration project

Identification of Health R&D Demonstration Projects

The demonstration projects

These projects should aim at developing health technologies (medicines, diagnostics, medical devices, vaccines, etc.) for diseases that **disproportionately affect developing countries and for which identified R&D gaps remain unaddressed due to market failures.** The projects must demonstrate effectiveness of alternative, innovative and sustainable financing and coordination approaches **to address identified R&D gaps.**

- **The Visceral Leishmaniasis (VL) Global R&D & Access Initiative** - Drugs for Neglected Diseases initiative (DNDi), submitted via AFRO and EMRO.

- Demonstrate that Health R&D can be **boosted** through:
  - **a) collaborative cross-regional coordination**,
  - **b) innovative & sustainable approaches for R&D** (i.e: drug accelerator)
  - **c) innovative sustainable financing mechanisms** (i.e: pool funding)
- **Guiding principles/CEWG**: Sharing knowledge; Equitable access; Sustainable funding; Exploring innovative incentives mechanisms

EDCTP

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Visceral Leishmaniasis Demonstration Project - WHO

- **Objective 1**: To develop **new safe and effective oral treatments** as monotherapy and as early as possible as combination treatment and a very safe, short-course one for **contacts and asymptomatic** careers once their role in transmission has been established.
- **Objective 2**: To develop technology of diagnostic (xenodiagnoses coupled with a quantitative PCR) in order to evaluate the **role in transmission of asymptomatic careers and PKDL patients**.
- **Objective 3**: To develop a **treatment for PKDL** (medical product).
- **Objective 4**: To support development of a shared, **open-access data base** to identify determinants of treatment effectiveness.

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