# *Leishmania* Vaccine Development:
## *Progress and challenges in the context of other control strategies*

*Farrokh Modabber, Ph. D.*
*Senior Advisor, Leishmaniasis*

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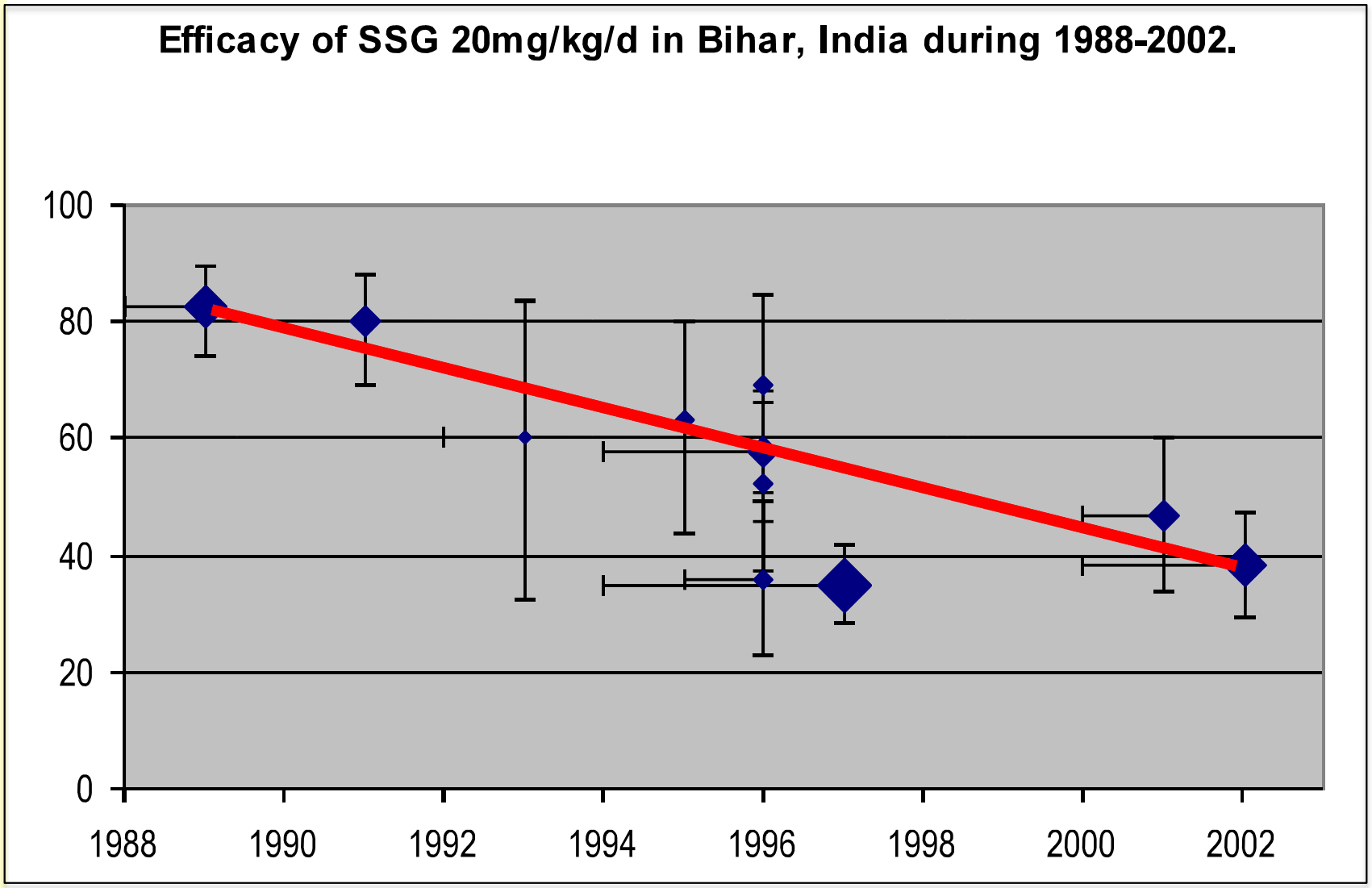
Drugs for Neglected Diseases *initiative*

# Decreasing SSG efficacy for VL treatment

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# Lots happened for VL management

1. New drugs & treatments: Miltefosine, Injectable Paromomycine, AmBisome, Drug combinations

Most significant advance:

Single-dose 10mg/Kg AmBisomefor visceral leishmaniasis in India.

Sundar S, et al. N Engl J Med. **362**:504-12. 2010

Cure rate after 6 mo FU: **95.7%** (95% CI, 93.4 to 97.9)

Yes, Can be used in rural hospitals in Bangladesh 97% cure rate, No SAE

*Dinesh Mondal,et.al.* www.thelancet.com/lancetgh
http://dx.doi.org/10.1016/S2214-109X(13)70118-9

Cost negotiated by WHO-MSF and Gilead to about $120/typical patient

Local production in India, to be improved and may create competitive pricing

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# Drug Combination for VL (DNDi Trial)

## Sundar S, et. al. Lancet, **377**(9764):477-86, 2011

| Treatment: Drug Combination Trial | Ampho-B 30 days in Hospital 15 injections | AmB 5mg/Kg x1 + Paro. 10X (11 days) | AmB 5mg/Kg x1 + Milt. X 7 (8 days) | Paro. 10x + Milt. X 10 (10 days) |
|---|---|---|---|---|
| Final cure (ITT) 95%CI FU 6 months | **93.0%** 87.5, 96.3 | **97.5%** 93.3, 99.2 | **97.5%** 93.2, 99.2 | **98.7%** 95.1, 99.8 |

Estimated costs US$ at 2008. Meheus F, et.al. PLOS Neg Trop. Dis. 7;4(9). pii: e818

| Strategy | Drug cost | Other direct medical | Non-medical & indirect | Total cost |
|---|---|---|---|---|
| L-AmB + MF | 95.7 | 14.8 | 12.8 | 123.4 |
| L-AmB + PM | 87.1 | 20.5 | 25.3 | 132.9 |
| MF + PM | 29.5 | 19.5 | 23.8 | 72.9 |
| L-AmB 10 | 140.0 | 11.0 | 2.5 | 153.4 |
| SSG | 57.8 | 40.7 | 73.4 | 171.8 |

Not as efficacious in Africa.
WHO recommend: SSG+ Paromo
Trial supported by DNDi – done by Leish E. Africa Platform

# New Developments

2. Commitment to eliminate VL (<1/10,000) in India, Nepal & Bangladesh by 2015? (availability of drug and diagnostic; daily payments to hospitalized patients in India, vector control; awareness, etc.

3. Serious drug development program for VL (DNDi with major Pharma). NCE's identified and being developed

4. Significant reduction in incidence of disease in major foci, India, Bangladesh, Nepal, Sudan, Kenya, Ethiopia, Uganda (LEAP), Brazil

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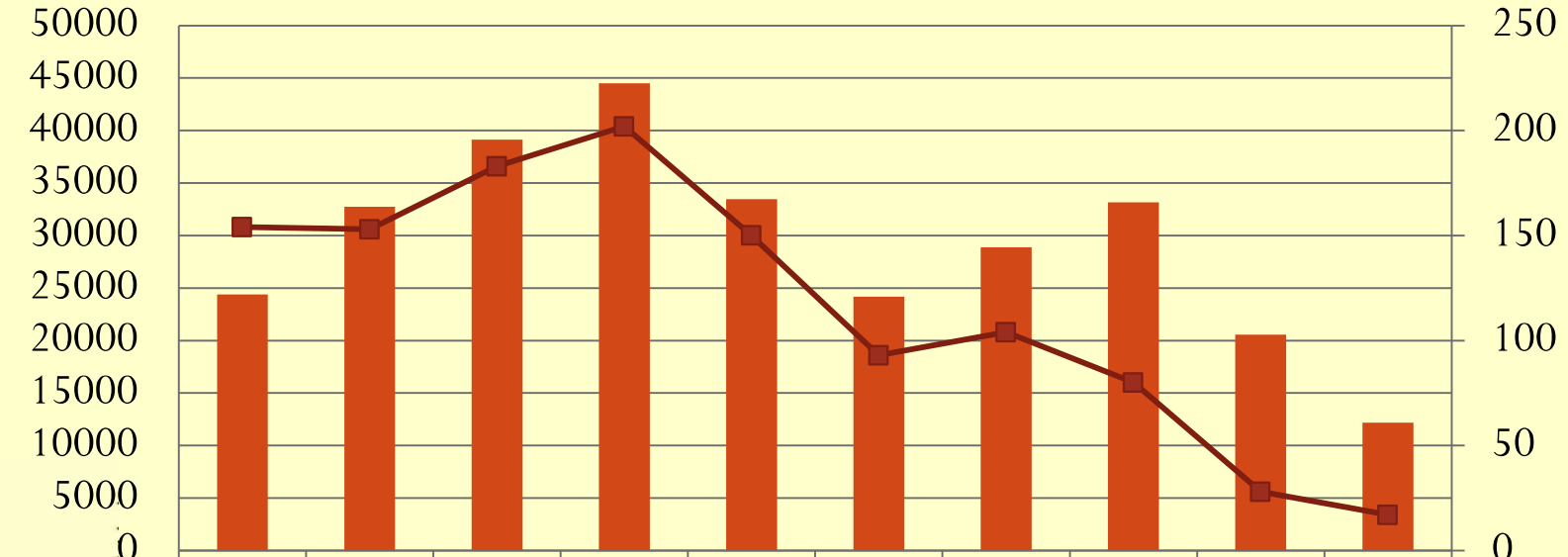
# "Reported" Incidence of VL in India

Dr Pradeep Das, Director, (RMRIMS), ICMR,
Ministry of Health and Family Welfare, Patna, India




| | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 (Oct) |
|---|---|---|---|---|---|---|---|---|---|---|
| Case | 24401 | 32740 | 39145 | 44508 | 33461 | 24167 | 28885 | 33155 | 20571 | 12193 |
| Death | 154 | 153 | 183 | 202 | 150 | 93 | 104 | 80 | 28 | 17 |

Factors responsible for decline:

Natural cycle (trough – unknown reasons)

Impact of treatments (Miltefosine, AmBisome) MSF, National Prog.

Elimination program: payment to patients, vector control

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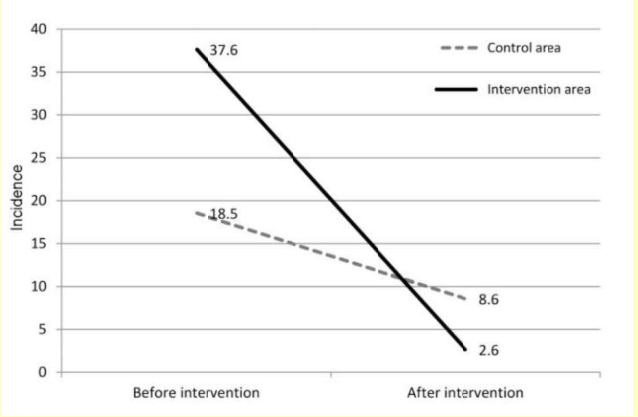
# Reduced Incidence of VL in High endemic Foci

**Bangladesh:**
75/100 upazilas achieved <1 case/10,000 2012
*40/100 Upazila reported 0 case till Aug. 2013*
*Shah Golam Nabi, Progrmme manger , DGHS, Mohakhali, Dhaka).*

**Nepal**: Yearly reduction in incidence, lately ± 200/yr

East Africa: > 50% reduction in cases
mortality highly reduced

1995-2005 LEAP countries (Sudan Kenya, Ethiopia, Uganda) had 40,000 VL cases/year (20,000 from Sudan)
with a mortality of about 4000 cases/year
In recent years there are less than 50% with very low mortality *(Head of LEAP, Dr A. M. Musa).*

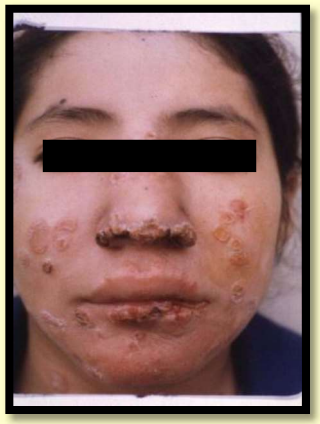


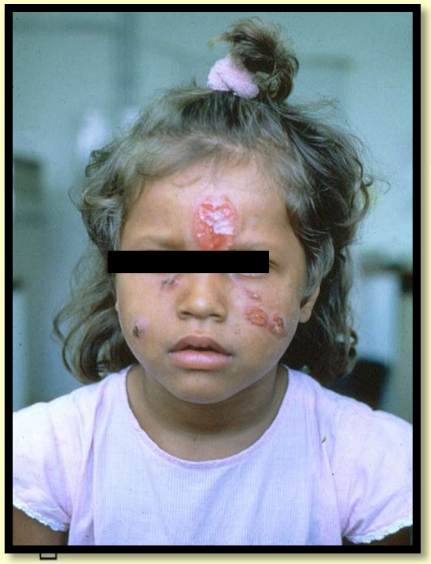

Vector control is controversial, but here a Demonstration project
Community-based insecticide impregnated Bed net.
Mondal, et al.'s EID Journal:
Volume 19, Number 7—July 2013

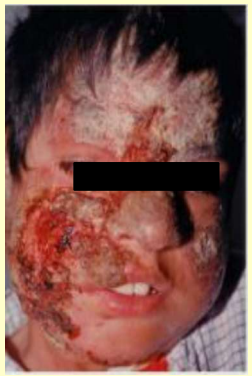
# Cutaneous Leishmaniases (CL) A neglected among Neglected Diseases – No Progress!

**New World**

L. amazonensis
L. (V) braziliensis
L. (V) guyanensis
L. Mexicana
L. (V) panamensis
L. (V) peruviana
L. chagasi (infantum)

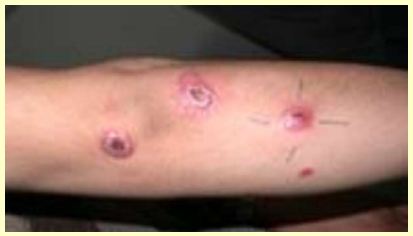


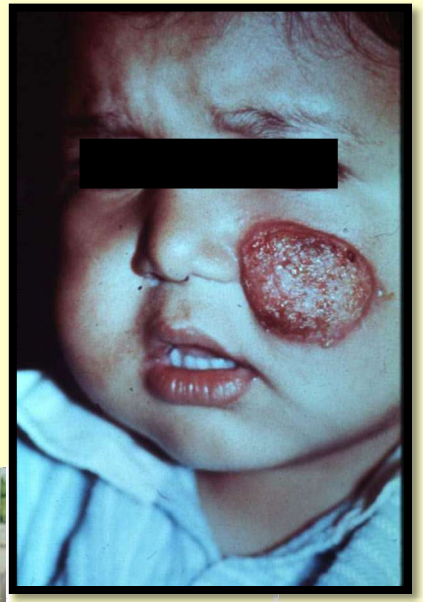


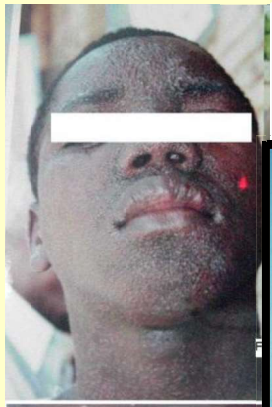


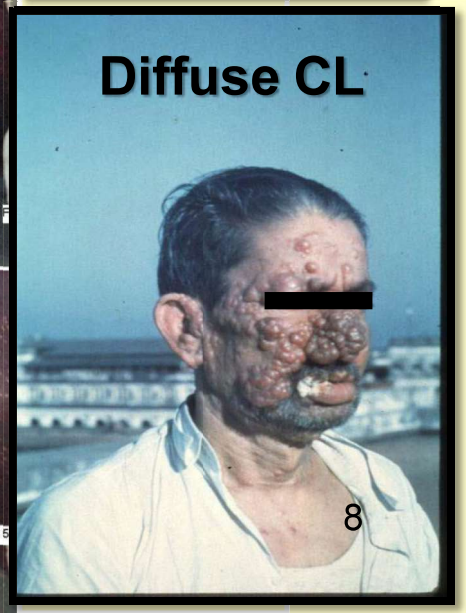
**Old World**

L. aethiopica
L. major
L. tropica
L. Infantum








Estimated 1,500,000 cases / year

GVIRF Bethesda March 2014

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# Human vaccines in clinical trials: Past

Past: First Generation Vaccines (Prophylaxis)

Killed parasites with or w/o BCG →Safe but no prophylactic efficacy

Addition of alum: (Alum-ALM+ BCG → ↑ CMI, not Ab!

One Phase-2 prophylactic trial in Sudan against VL:

544 randomized to single injection of Alum-ALM+BCG or Diluent.

2 year Follow up:

0 case in Vaccinated *vs* 4 in control

(Needed more studies, but not continued)

*Khalil EA, et al. Ann Trop Paediatr.* ***26****:357-61, 2006.*

Issues: Use of FCS to grow parasite, Standardization & BCG lesions, …

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# Second Generation Vaccines
# IDRI's vaccine: First defined r-Poly-Protein


IDRI Vaccines: Prophylactic and therapeutic efficacy in mice against challenge by needle but not by sandfly (C57 Bl), protective in Balb/c. Safe and Immunogenic (Phase-1trials in US and India).

Trials in Colombia, Brazil (CL), Peru (ML), *Accelerated time to cure in CL and ML patients when used in combination with chemotherapy*

Trials against PKDL & DCL showed No therapeutic efficacy with or without chemotherapy.

New vaccine focused on VL: KSAC+ GLA - SE being developed

**Is a TLR-4 agonist a good adjuvant for human leishmaniasis???**
In mice, CpG (TLR-9 agonist) enhances MPL-SE activity

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# York University- Adenovirus vector with 3 genes of *Leishmania*
# Phase-1 completed, awaiting further trial (Prof. Paul Kaye)

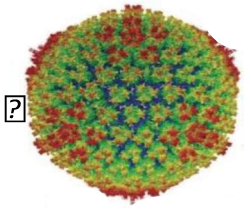
## ChAd63-KH: a new therapeutic vaccine for VL/PKDL

*Program PI: Paul Kaye*

*The insert….*


Engineered to reflect strain diversity in SE Asia/E. Africa

*The viral vector….*



**ChAd63**

- produced in suspension culture Procell92 cell line for scalable manufacture
- Safety and immunogenicity data available from hundreds of volunteers

*Preclinical proof of concept….*

The Journal of Infectious Diseases

- Maroof et al. *JID.* 2012. **205**:853–63

*The clinical trial….*

| LEISH1: A study to assess the safety and immunogenicity of a new Leishmania vaccine candidate ChAd63-KH | |
|---|---|
| ISRCTN | ISRCTN07766359 |

**Phase 1 first -in-human study: dose escalating, "prime only"**

- Excellent safety profile confirmed
- Excellent levels of $CD8^+$ T cell responses (breadth/magnitude/% responders)

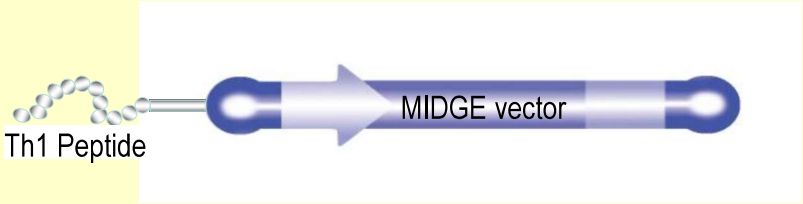
# LEISHDNAVAX

## Prevention and therapy of all forms of leishmaniasis

*(Provided by Dr Christiane Juhls, Mologen on behalf of Consortium)*

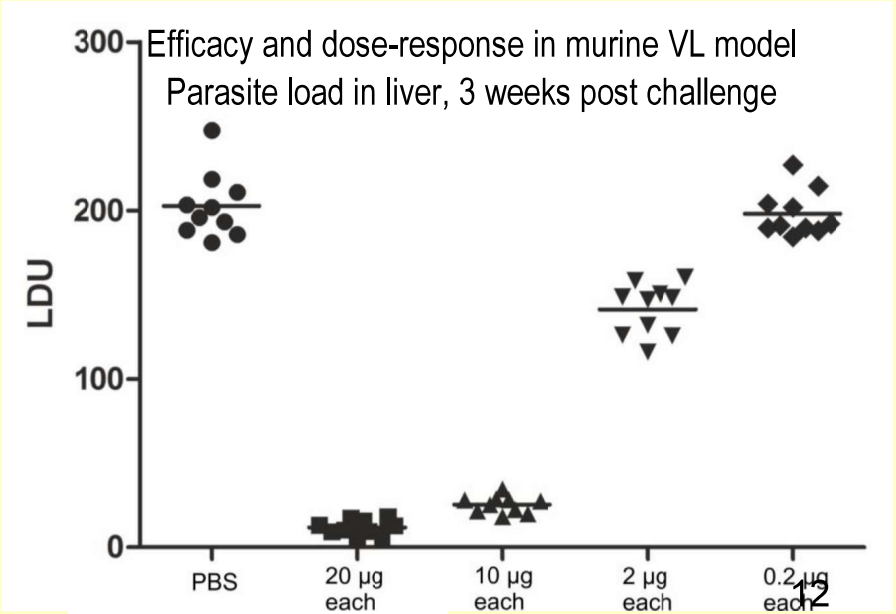
**Vaccine: No clinical studies yet**

Mixture of 5 highly conserved, highly immunogenic *Leishmania* antigens encoded by small minimalistic linear DNA expression vectors




**Ready to enter clinical Phase 1 trial:**

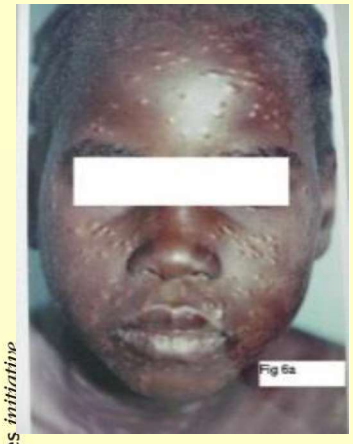
- ✓ Preclinical efficacy and safety proven
- ✓ CD4 and CD8 T cell responses against all 5 antigens detected in target populations
- ✓ Clinical sites (VL, India & CL, Tunisia) selected, study plan outlined, clinical immuno-monitoring established
- ✓ Indian pharmaceutical partner identified




S. Das, S. Roy, IICB Kolkata

# Vaccine or Immune Res. Modifiers (IRM) for Therapy

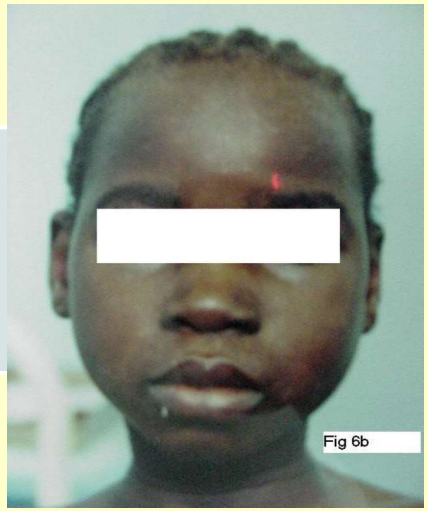
- Used in therapy (Convit et. al. Venezuela in thousands of patients)
- Alum-ALM+ BCG + antimonial on persistent PKDL, difficult to treat with drugs alone. PoC trial.




| Day | Drug alone | Drug + Vaccine |
|---|---|---|
| 60 | 8/15 (53%) | 13/15 (87%) |
| 180 | 6/15 (40%) | 15/15 (100%) |
| (Final) | 2 relapsed | All cured |

p<0.004

*Musa AM, et al.. Trans R Soc Trop Med Hyg. 2008; **102**:58-63.*




Musa A et.al. Trans. Roy. Soc. of Trop. Med. & Hyg. **102**, 58—63, 2008

- Can also be used to reduce dose of drug

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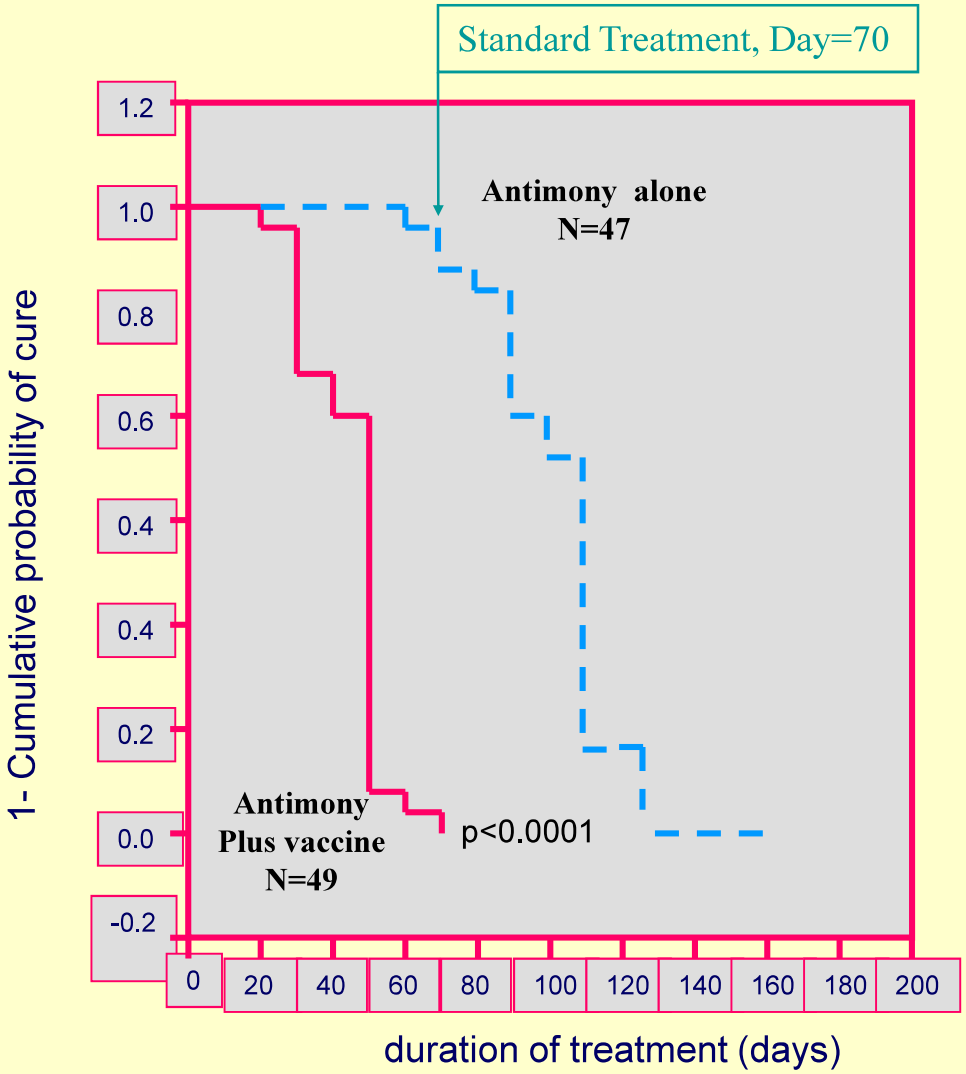
# Immunotherapy of CL in Brazil

Machado—Pinto J. *et al. Int. J. Dermatol.* ***41***:73-8, 2002




Mayrink's vaccine
registered as adjunct to
low –dose antimony
In Brazil, but not used

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# Progress in Control of Cutaneous Leishmaniasis

## No Major Advance

Situation: Increased resistance to Antimonials, (R-*L.tropica* isolated)

Increased incidence due to war, population displacement

Other control measures have failed

No acceptable, affordable and safe treatment is available
AmBisome, Miltefosin (costly, variable results), thermotherapy, …
Unsatisfactory

<u>Need vaccine and Immune Response Modifier to enhance cure:
to shorten time to cure, reduce scars.</u>

**Opportunities**:

1- CpG as adjunct to chemotherapy. D-35, D. Verthelyi, et al. NIH/FDA

2- Live challenge to evaluate vaccines (needle infection standardized for *L. major*, can be done in certain foci (without HIV)

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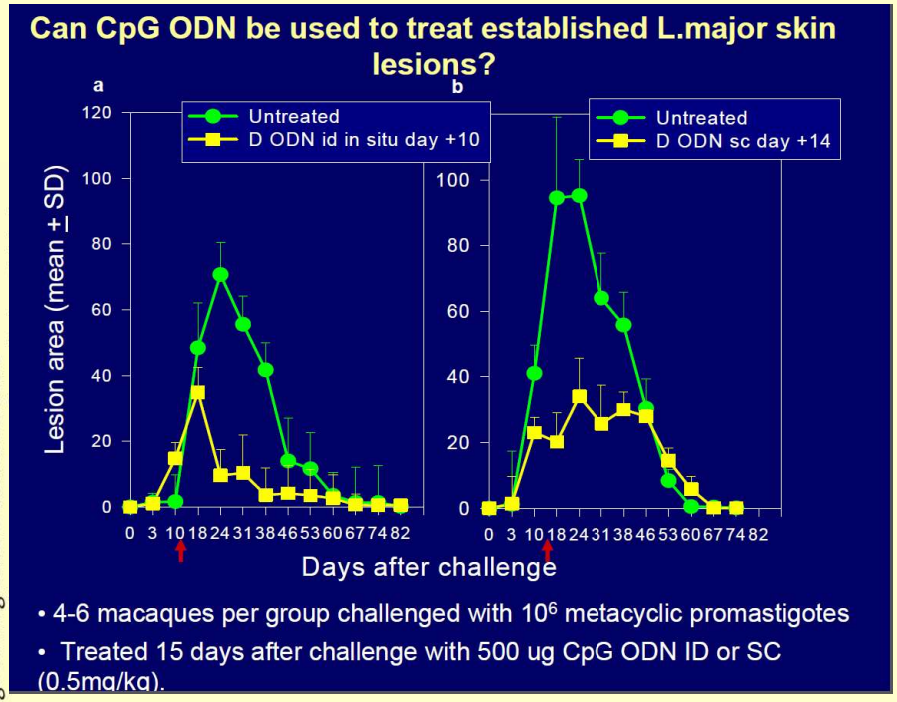
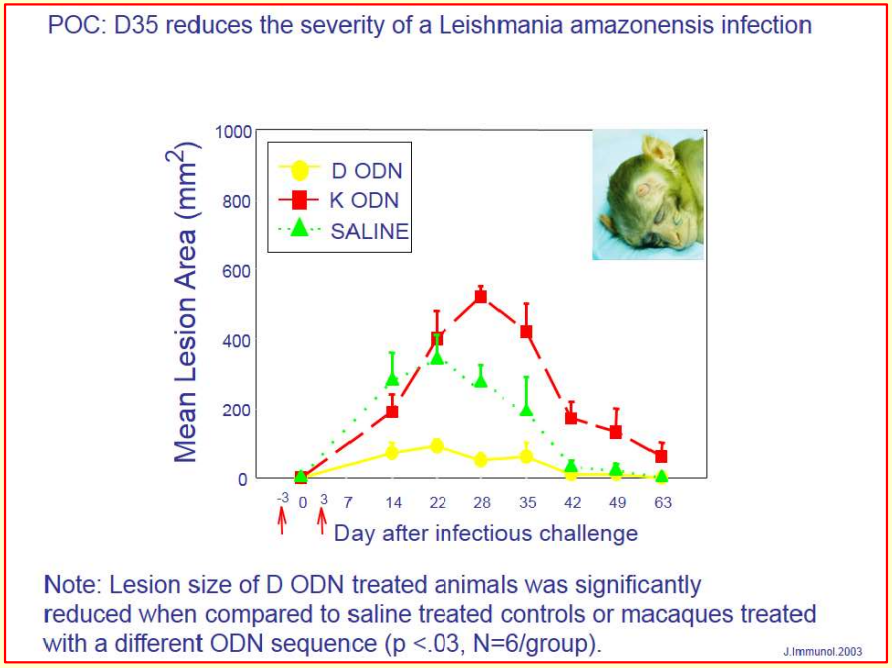
# Immune Response Modifier as Adjunct to Therapy

Flynn B[1], Wang V, Sacks DL, Seder RA, **Verthelyi D.**
Prevention and treatment of cutaneous leishmaniasis in primates by using synthetic type D/A oligodeoxynucleotides expressing CpG motifs.
. Infect Immun. 2005 Aug;73(8):4948-54.

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GVIRF Bethesda March 2014

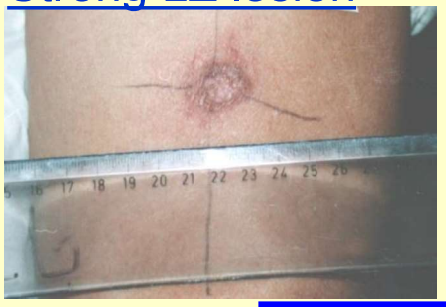
Daniela Verthelyi, et. al.
FDA

Leishmanization an ancient practice also used in Israel, Uzbekistan and Iran

**Standardized for live challenge studies in Iran** *(Khamesipour, A, et al. Vaccine 23:3642-48. 2005)*

Seed Bank & Stabilates from well characterized *L.major*

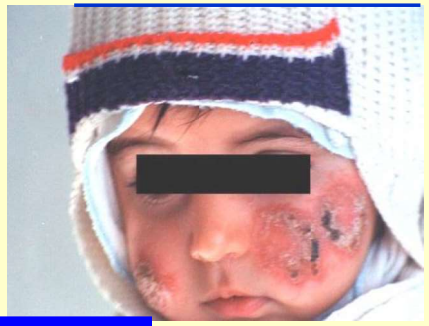
Strong LZ lesion



Iran

18 volunteers injected with live *L. major* followed for 1 year

Natural infection



**All developed lesion and all lesions healed**
**Mean duration to scar formation= 166.6 days (SD =67.65)**

14 recovered Volunteers injected again
+ 4 new volunteers

**14/14 protected no ulcer = 100% protection**
**4/4 developed lesion, healed in 142.00 days (sd=88.30)**

In larger Leishmanization programs, there were 2-4 % reinfection.
About 50/1000,000 developed non-healing (recorded) .

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# Vaccine Needs

- **For VL** *Short term*: Implement available control measures

  *Long term*: An affordable field friendly safe live vaccine: Much like BCG, smallpox vaccine
- One candidate: Live attenuated (i.e. p27-KO *L. donovani, Nakhasi, Fujiwara et al.* Better than registered vaccine for dogs.
- Consider cost of development and implementation for all vaccines.
- **For CL**, Vaccine is urgently needed, since there are no effective control measures. Use leishmanization as challenge to evaluate candidate vaccines quickly & cost-effectively. (must be done with caution in HIV- free foci). All participants are protected either by candidate vaccines or leishmanization.

# THANK YOU

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# For Discussions
# vaccine requirements

Anti-infection, anti-disease

How many injections, annual booster?

Dead vs. live vaccine: p27-KO (Attenuated) *L. donovani,* (H. Nakhasi, Fujiwara et al.)

Live challenge? Leishmanization for CL, *L. donovani* (Rescue with Ambisome)???

Therapeutic, vs. Prophylactic

Broad spectrum (Anthroponotic CL, Zoonotic CL).

Can Canine vaccine protect humans. P-27 KO was better than commercial dog vaccine

Cost of development & cost of implementation *vs* other control measures

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| VL cases | Reported | Estimated | Population at risk/Total (Mil) (fm guesstimate) |
|---|---|---|---|
| L. America | 3668 | 4500- 6800 | 20-40 / 597 |
| East Africa | 8569 | 29400-56700 | 15-20 / 214 |
| Mediterranean Region* | 875 | 1200-2000 | 25-40 / 370 |
| West-Central Asia (M.E.)* | 2496 | 5000-1000 | 20-40 / 442 |
| Indian Sub-continent | 42623 | 162100-313600 | 200-350 /1418 |
| Total | | 200,000 | 280 / 3041 |

| | |
|---|---|
| **Cost of Treatment** | **$200 x 200,000 P= 40 M** |
| Cost of vaccination | $5/dose x 2 inj for 28M = 280**M**** |

*L. infantum/chagasi*

** Assuming 100% protection with 2 injections in 10% of population at high risk

Some data adopted from **Alvar J, Velez ID, Bern C, et al. PLoS ONE 7(5): e35671.2012**

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