Kala-azar: Can Visceral Leishmaniasis Ever Be Controlled?

R. Killick-Kendrick
Honorary Research Investigator
(Division of Biology, Imperial College, London, UK)

Global Health Histories Series
Tropical Diseases: Lessons from History
The Burden of the Leishmaniases

All forms:

Global prevalence: ~12 million cases
Annual incidence: 1.5 - 2.0 million
Countries affected: 88
People at risk: 350 million
Visceral Leishmaniasis alone

- Estimated Disability Adjusted Life Years: 2 million
- Estimated new symptomatic cases annually: 500,000
  (90% in East Africa, Brazil and the Indian subcontinent)
Distribution of the Visceral Leishmaniasis
East Africa
Patient with visceral leishmaniasis in a Médecins sans Frontières clinic in East Africa.

Photo: Ed Rowton, Walter Reed Army Institute of Research
Acacia seyal woodland in Eastern Sudan, the habitat of the Sudanese vector of visceral leishmaniasis (*Phlebotomus orientalis*)

*Photo: R. Killick-Kendrick*
“Should an extensive outbreak of kala-azar occur in any village, the whole village should be burnt and a new village built on a fresh site, after the patients and contacts have been isolated.”

Thomson, D.S.B. (1910). Kala-azar Commission to investigate the prevalence and cause of the disease in Eastern Sudan; (1) General report.
No control programme has so far been implemented in Sudan. Important questions concerning epidemiology, entomology and animal and/or human reservoir must first be answered.'

(Zijlstra and El Hassan, 2001)

Seventeen to twenty months later, clinical cases had fallen by 59%.

It was estimated that the intervention prevented 1,060 new cases ---

and the mean protection effect was 27%.

(Ritmeijer et al. 2007)
In March, 2009, aid agencies were expelled from northern Sudan.

Médecins sans Frontières was obliged to cancel plans to control visceral leishmaniasis in the east of the country.
Brazil
Visceral leishmaniasis caused by *Leishmania infantum* with a canine reservoir (Brazil).

(L = liver; S = spleen)

*Photo: W. Peters*
Distribution of visceral leishmaniasis in Brazil, 1984

Deane & Grimaldi, 1985
Poor rural housing in north east Brazil
An urban focus of visceral leishmaniasis in north-east Brazil

Photo: P.D. Ready
Last stages of canine leishmaniasis with severe emaciation and depilation

Photo: R. Killick-Kendrick
Control by culling seropositive dogs (1)

Brazil Control Programme 1984-1996

- Sera of 6.5 million dogs tested
- 153,819 seropositive dogs destroyed
- One million houses sprayed with insecticide
- Cost >US$ 96 million
Serologically positive dogs culled to control visceral leishmaniasis

Photo: R. Killick-Kendrick
Culling serologically positive dogs as a means of control: reasons for failure

- Resentment by dog owners,
- Inability of the tests to reveal all dogs that are infectious to sand flies,
- Delay between testing and culling,
- And, in some places, the possible presence of other reservoir hosts.

(Oliveira et al., 2008).
Clinical signs reveal only a small proportion of dogs with CanL: serology and/or PCR reveal many more without clinical signs (but able to infect sand flies).

Field trial to reduce risk of infection with VL in São Paulo State, 2002-2005

- All seropositive dogs in a chosen cohort were killed
- 22,260 seronegative dogs were fitted with deltamethrin-impregnated collars, changed annually
- From 2002 to 2005, the prevalence of canine infections fell from 12.5% to 3.9%
- During the same period, the incidence of human cases fell from 34.1/100,000 to 5.4/100,000

(Camargo-Neves et al., 2004, 2009)
Changes in the prevalence of CanL and the incidence of human VL in two study sites in Brazil after collar ing all seronegative dogs in April 2002

India
The habitat of *P. argentipes* in a focus of anthroponotic visceral leishmaniasis in Bihar State, India.

Photo: R. Killick-Kendrick
Anthroponotic visceral leishmaniasis; Bihar State, India; the spleen (S) and the liver (L) are greatly enlarged.
Post kala-azar dermal leishmaniasis of the thigh showing depigmentation and a skin rash; the skin is heavily infected: these patients are reservoirs of infection. Bihar State, India.

Photo: R. Killick-Kendrick
Treatment of kala-azar in India (1)

Urea stibamine introduced in 1922

Many thousands of cases successfully treated

Survival much improved

But little measurable effect on prevalence of infection

(H.E. Shortt, 1932)
Treatment of kala-azar in India (2)

‘In hyperendemic areas of India, no more than 9% of those affected with VL seek medical advice for diagnosis and/or treatment.’

‘Owing to lack of resources and health education, compliance with treatment is extremely low.’

(P. Desjeux 2001)
Treatment of kala-azar in India (3)

**Pentostam:** resistance widespread

**Ambisome:** intravenous infusion, average cost for two injections: US$ 250: one injection treatment, under investigation, average cost: US$ 125

**Paramomycin:** intramuscular injections for 21 days, average cost of drug: US$ 15-20
Treatment of kala-azar in India (4)

**Miltefosine**: oral twice daily for 28 days; contraindicated in pregnancy; long half life and therefore fears for resistance of parasite; not yet known if it cures PKDL

Guidelines on use of Miltefosine, Govt. of India
Treatment of kala-azar in India (5)

Mean household expenditure for one case of VL in Bihar is estimated at US$ 59.8.


‘In Bihar State, 75% of VL patients have a daily income of <US$ 1.’

(Desjeux, P. 2001)
‘DDT is cheap, but its harmful and long-lasting environmental effects require proper evaluation; it may not in the end be the insecticide of choice for long-term control.’

(Thakur, 2000)
Limitations in house spraying with DDT (2)

Operational deficiencies

‘--- despite the supposed 5 DDT spray-rounds between 1992 and 1994, 57% of houses had not, in fact, been sprayed.’

(Thakur, 2000)
Limitations in house spraying with DDT (3)

Insecticide Resistance

In Bihar, *Phlebotomus argentipes* developed resistance to DDT during house spraying in the epidemic in the 1970s

(Singh *et al.*, 2001)
Danger of post-spraying epidemics.

When house spraying is abandoned prematurely, the population of sand flies recovers quickly and an epidemic is highly probable.

This happened in India in the 1970s after the campaign to eradicate malaria worldwide was abandoned 1969

(Sen Gupta, 1975, Makhopadhyay et al., 1987).
Can Visceral Leishmaniasis Ever Be Controlled?

YES
Distribution of visceral leishmaniasis in China in 1958 before the control campaign

Xu Zhi-biao (1988)
All dogs were destroyed

All houses sprayed with either DDT or Gammexane annually for 30 years

Annual active case detection and treatment
Distribution of visceral leishmaniasis in China in 1988 after the control campaign

Xu Zhi-biao (1988)
Lessons (1)

ESSENTIALS

Peace

Political Commitment

Long-term Funding

Feasible Strategies

Public Education
Lessons (2)

Structure of the Focus

Distribution and Incidence

Population dynamics and behaviour of vector(s)

Identification and behaviour of animal reservoir(s) (if appropriate)
Lessons (3)

Action against the source of infection

Destroy stray dogs: protect all other dogs from sand fly bites with insecticide-impregnated collars or by dipping in insecticide

Active case detection and treatment including PKDL patients (How?)

Asymptomatic cases?
Lessons (4)

*Action against the vector*

- Efficient and supervised house spraying
- With more than one insecticide
- Regular tests for insecticide resistance
- Insecticide-impregnated bed-nets
Thank you