The challenge of sustaining elimination, role of asymptomatics and PKDL

Consortium: Setting the Post Elimination Agenda for Kala-Azar in India (SPEAK India)
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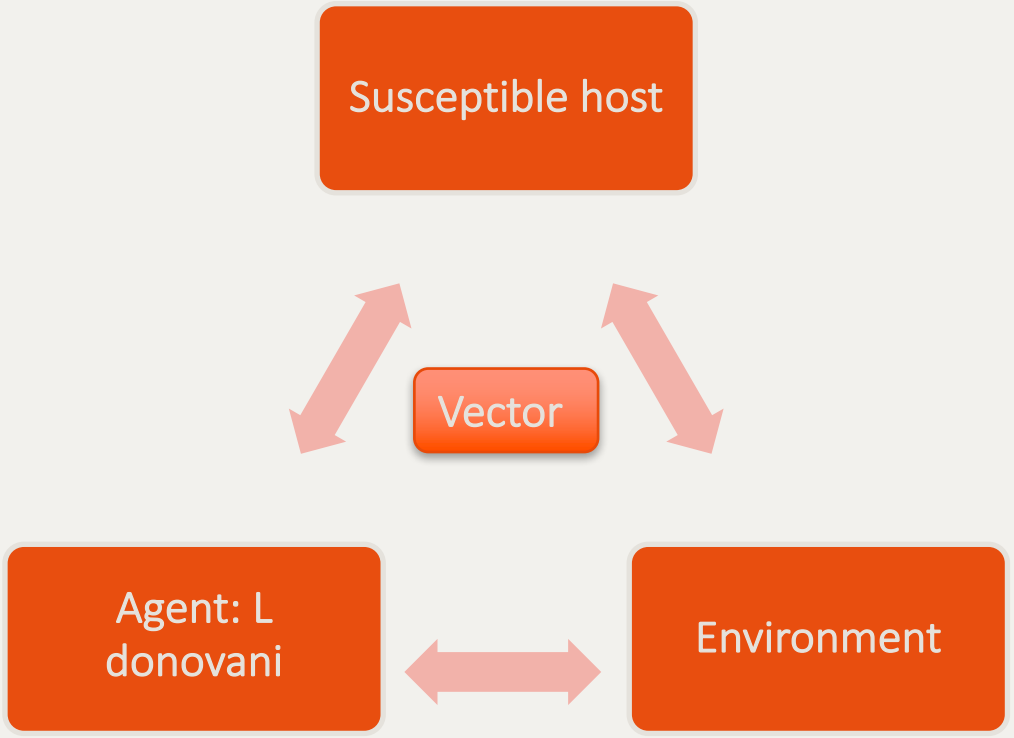
Epidemiological triad in visceral leishmaniasis

Immune status, HIV, malnutrition, poverty, age, genetic factor



Reservoirs: VL, HIV-VL, PKDL, asymptomatic, relapsed case

Breeding sites, poor housing and sanitation, migration, climate change, new settlements,

Asymptomatic leishmanial infection (ALI)

- Currently there is no reference standard or appropriate biomarker
  - Serological test: rk39 ICT, rk39 Elisa, DAT
  - PCR, qPCR
  - LST
- Increase proportion of ALI to VL:
  - Bangladesh: 4 :1. (Bern 2007)
  - India/Nepal: 8.9: 1 (Ostyn 2014)
- Risk factors associated with VL also associated with ALI
- Progression of ALI to VL:
  - Proportion progressing to symptomatic disease within one year ranged 1.5–23%
  - strongly associated with initial sero status (high titers) and with seroconversion;
  - high titer DAT convertors, the hazard ratio as high as 97.4 (compared to non-convertors)

Comparative results of PCR, DAT and rK39 ELISA from India and Nepal (Srivastava 2013)

	PCR positives: % (N)	DAT positives: % (N)	rK39 ELISA positives: % (N)‡
India			
HNK	24.6% (37/150)	14.0% (21/150)	18.1% (27/149†)
HHC	20.6% (20/97)	14.4% (14/97)	19.5% (19/97)
HPK	23.0% (9/39)	89.0% (35/39)	74.3% (29/39)
Total	23.1% (66/286)	24.5% (70/286)	26.3% (75/285)
Nepal*			
HNK	17.6% (32/182)	5.4% (10/182)	NA
HHC	12.5% (3/24)	20.8% (5/24)	NA
HPK	26.1% (6/23)	95.0% (22/23)	NA
Total	18.0% (41/229)	16% (37/229)	NA

NA, not applicable; HHC, healthy household contacts; HNK, healthy non-kala-azar; HPK, healthy past kala-azar.

Groups		% Positive AI	% Negative AI
HNK	PCR *vs.* DAT	17.9 (5.5–30.2)	36.0 (27.1–44.8)
	PCR *vs.* ELISA	20.9 (5.5–36.2)	25.0 (17.3–32.6)
	DAT *vs.* ELISA	15.8 (2.0–29.5)	27.6 (19.6–35.5)
HHC	PCR *vs.* DAT	17.0 (0.5–33.4)	30.8 (20.4–41.0)
	PCR *vs.* ELISA	20.1 (2.5–37.6)	29.5 (19.2–39.6)
	DAT *vs.* ELISA	16.6 (0.0–33.3)	29.4 (19.3–39.5)
HPK	PCR *vs.* DAT	36.7 (5.2–68.2)	5.8 (0.0–14.1)
	PCR *vs.* ELISA	35.2 (4.0–66.4)	13.3 (1.1–25.4)
	DAT *vs.* ELISA	81.3 (67.1–95.5)	37.3 (7.3–67.2)

Agreement indices (AI) between PCR, Direct Agglutination Test

Asymptomatic leishmanial infection (ALI) II

- Are ALI infectious:
  - Mathematical modelling suggests that they constitute a reservoir of parasites driving the epidemic (Staunch 2011)
  - Asymptomatic infected persons in early stages of HIV infection were able to infect sand fly (Molina 1994)
- Do we have the drugs to treat asymptomatic otherwise healthy individuals?
- What is needed?
  - Standardized definition, validated biomarkers/ diagnostic tests.

Post Kala-azar Dermal Leishmaniasis (PKDL)

- Incriminated in the resurgence of VL in India in the 1970s following discontinuation of insecticide spraying
- Case definition:
  - Probable: Skin lesion+ (Person living in endemic area + rk39+ve)
  - Confirmed: Probable + parasitology+ve.
- Prevalence of PKDL: few prospective cohort studies conducted
  - Bihar: Probable, 7.8/10,000 and Confirmed, 4.4/10,000 population (Singh 2012)
  - Bengal: 1% point prevalence (Ganguly 2015)
  - Bangladesh: 3.8-7.3 /1000 population (Rahman 2010)
- Interval between treatment of VL and onset of PKDL: 6 months -3 years or longer (14 yrs).
- Up to 27.5% of KA cases developed PKDL in Bengal. (Ganguly 2015)

Post Kala-azar Dermal Leishmaniasis (PKDL) : Diagnosis and Treatment

- Case finding: No standardized validated active strategy. Delay in diagnosis even with active approach.
- Diagnostics: limitations in the field
  - SSS: Macular very low; Papulo-Nodular – 20 to 40% (Ramesh 2015; Singh2015)
  - Biopsy: Macular Macular 40%; PN 91% (Verma 2015)
  - qPCR: 96-100% (Kumar 2009)
- Treatment PKDL: prolonged and difficult
  - Miltefosine for 12 weeks
  - Amphotericin B 60-80 inj
  - LAMB 3 weeks.

PKDL and transmission

- 1933 Napier: Parasites demonstrated in sand flies feeding on 2 patients with nodular.
- 53% of sand flies that fed on 4 PKDL patients with nodular or nodulo-ulcerative lesions developed infection (Addy 1992).
- VL outbreak in southern West Bengal in the 1980s implicated on PKDL (Addy 1992)
- PKDL and increasing drug resistance:
  - Increasing resistance to antimony in the 1990's was thought to be contributed by even more resistant strains in PKDL patients (Singh 2006)
  - Decline in Clinical Efficacy of Miltefosine in PKDL in India (Ramesh 2015)
  - In vitro susceptibility towards miltefosine of parasites isolated after relapse was significantly lower (>2 fold) in comparison with the pre-treatment isolates ($P<0.005$).

Conclusion

- Elimination of kala-azar as a public health problem target is not only to be achieved but sustained as almost all of the variables in the transmission triangle will continue to exist.
- Better understanding on the role of the ALI and PKDL needs to be defined
- Development of tools for diagnosis and appropriate safe treatments would be required if these entities are proven to play a significant role in the transmission..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Drugs for Neglected Diseases initiative
Thank you